NEW YORK STATE JOURNAL OF MEDICINE

JANUARY 1984 • Volume 84, Number 1

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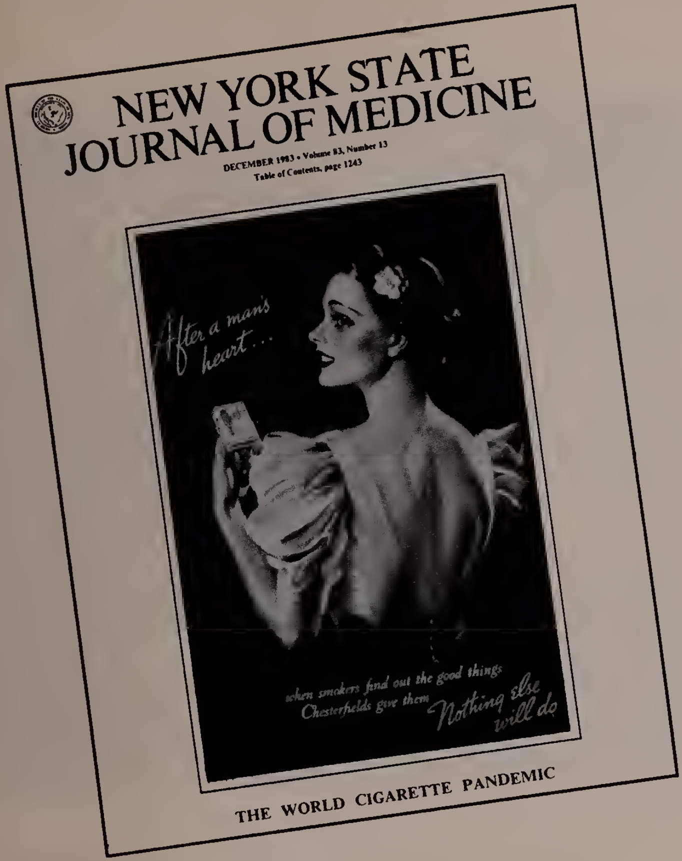

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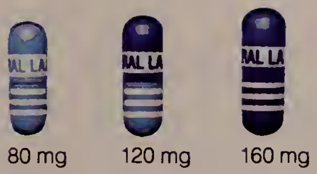

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DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.

CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

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INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity.

In dosages greater than required for beta-blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain.

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block; 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL

WARNINGS. CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

> IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. General: Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic. pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported

Miscellaneous. alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized.* The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily.

PEDIATRIC DOSAGE — At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

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JOURNAL OF MEDICINE

January 1984 • Volume 84, Number 1

COMMENTARIES

Thrombolytic therapy in thromboembolic disorders of the lung

The role of thrombolytic therapy in the treatment of thromboembolic disease of the lung has remained a controversial subject since urokinase and streptokinase became available for general clinical use in 1977. The Urokinase Pulmonary Embolism Trial[1] showed that although systemic urokinase administration led to accelerated resolution of pulmonary emboli in comparison to heparin, no difference was noted in short-term mortality between the treatments. Bleeding complications were appreciably higher in the patients receiving thrombolytic therapy. Furthermore, although urokinase administration led to radiographic and pulmonary hemodynamic improvement in comparison to heparin therapy, the changes, while statistically significant, were neither clinically nor physiologically important enough to justify routine use of thrombolytic therapy.

The fibrinolytic system of blood consists of the proteolytic enzyme plasmin, its inactive precursor plasminogen, and plasminogen activator, present in various tissues and blood, that presumably originates from vascular endothelium. Also present is α_2-antiplasmin, a circulating inhibitor of plasmin activity. Normally, plasminogen activator is released by endothelial cells in response to various stimuli, including the presence of fibrin clots. Plasminogen activator then binds to fibrin, forming a complex that avidly binds and activates plasminogen to form plasmin, thereby allowing local fibrinolysis to occur at the clot surface. Interaction with α_2-antiplasmin is prevented as the binding sites on plasmin necessary for α_2-antiplasmin attachment are occupied by the fibrin-plasminogen activator complex.[2-4] The thrombolytic agents presently available form plasmin either by a direct effect on plasminogen (urokinase), or by first forming a complex with plasminogen which then converts free plasminogen to plasmin (streptokinase). However, these agents activate circulating as well as fibrin-clot associated plasminogen, causing systemic fibrinolysis and fibrinogenolysis, and, with it, a bleeding diathesis.[5]

In an attempt to circumvent this problem, Rijken and Collen[6] have purified extrinsic plasminogen activator from a cell line in culture. In a number of animal models they have shown that administration of this agent leads to substantial local fibrinolysis of autologous clots in the absence of systemic fibrinolysis.[7-9] Furthermore, intravenous infusion of the same plasminogen activator was successful in lysis of major renal and iliofemoral vein thrombi in two patients.[10] Human tissue-type plasminogen activator is not, however, clinically available, and although this material has been produced recently using recombinant DNA techniques,[11] controlled human trials in venous thromboembolism comparing plasminogen activator to streptokinase and urokinase remain to be done.

Another approach to minimize the propensity to bleeding attendant with systemic fibrinolysis has been the local, low-dose administration of thrombolytic agents. Intraarterial administration of streptokinase in low dosage has been successful in restoring blood flow in selected patients with coronary and systemic arterial thrombosis.[12-14] In an experimental model of jugular-vein thrombosis in the rabbit, local administration of urokinase allowed an equivalent degree of fibrinolysis to occur at one-tenth the total dosage given systemically with no change in chemical indices of general fibrinolysis, such as reduction in plasma fibrinogen or α_2-antiplasmin levels.[9] Local application of low-dose streptokinase was also effective in the lysis of extensive endobronchial blood clots formed following pulmonary hemorrhage, presumably by activation of plasminogen present in the clots.[15] Local administration of thrombolytic agents in low dosage is also possible in patients with pulmonary emboli. In an uncontrolled trial, Edwards et al[16] infused approximately 5% of the standard systemic dose of urokinase over two hours into the main pulmonary artery in eight patients with massive pulmonary emboli, and effected impressive hemodynamic improvement in six with no bleeding complications. The possible benefits of such treatment would have to be weighed against the other advantage of systemic fibrinolysis, that is, thrombolysis of the thrombus or thrombi from which the emboli originated, wherever the location.

Systemic administration of thrombolytic agents may also have previously unrecognized beneficial effects on the pulmonary circulation. Sharma et al[17] reported detailed pulmonary function evaluation in a series of patients with pulmonary embolism but without underlying clinical cardiopulmonary disease treated with urokinase or streptokinase and a similar control group treated with a standard heparin regimen. In both groups, approximately one third of the patients had massive pulmonary emboli defined as obstruction or filling defects involving two or more lobar arteries or their equivalent. In the group receiving thrombolytic therapy the diffusing capacity for carbon monoxide was normal at both two weeks and one year from diagnosis; in the heparin-treated group diffusing capacity remained abnormally low at both time intervals. Analysis of the determinants of diffusing capacity showed that in the heparin-treated group this difference was due to a reduction in pulmonary capillary blood volume. In the group given thrombolytic agents, pulmonary capillary blood volume was restored to normal. This report thus suggests that prompt, intensive thrombolytic therapy may have a beneficial long-term effect on the pulmonary microcirculation after thromboembolic insult.

Many clinicians have reserved use of thrombolytic agents for selected patients with documented massive pulmonary emboli and those with hemodynamic compromise following emboli.[18] If the data of Sharma et al[17] are confirmed in appropriate controlled trials, one may speculate that thrombolytic therapy may be beneficial in another group: patients with emboli in the presence of underlying pulmonary disease characterized in part by compromise of the pulmonary vasculature. In these disorders, including emphysema, interstitial lung disease, and recurrent multiple pulmonary emboli, thrombolytic therapy may help prevent or ameliorate further embarrassment of the pulmonary microcirculation with its attendant worsening of gas exchange and development of pulmonary hypertension. As further information on the efficacy of local administration of these agents becomes available, and if clinical trials using extrinsic plasminogen activator bear out the promise of the experimental studies, indications for thrombolytic therapy in pulmonary thromboembolism may be broadened.

RANDOLPH P. COLE, MD
Assistant Professor of Medicine
College of Physicians and Surgeons
Columbia University
630 West 168 Street
New York, NY 10032

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The APUD puzzle

The hypotheses associated with the acronym APUD (*a*mine *p*recursor *u*ptake and *d*ecarboxylation) have been helpful in integrating related cells in various anatomic sites. At one time it was hoped that all such phenomena—tumors producing a similar spectrum of chemicals—could be neatly explained by the hypothesis that they were the product of cells derived from unique neuroectodermal cells of the embryonic crest, but the situation is more complex.

Four reports in this issue of the *Journal* illustrate the diverse pathologic states associated with the neurocrest-APUD suppositions. The carotid body tumor described by Rosenkranz and Schell caused a clinical dysfunction by mechanical pressure rather than by the release of active substances produced by the tumor cells. Similarly, the rare aortocoronary paraganglioma reported by Orenstein, Green, and Kancherla threatened the life of the patient by encroaching on the coronary arteries.

On the other hand, it was the catecholamine products released from a tumor of the organ of Zuckerkandl which caused the fascinating syndrome reported by Kagali, Madani, and Bhitiyakul.

However, the inclusion by Jackson and Glassberg of an islet cell tumor that caused "pancreatic cholera" within the neurocrest-APUD complex may represent a false extension of the hypothesis.

Tumors from every germ layer and many diverse tissues have been reported to produce APUD products. The inference is that perhaps many malignant processes can be fixed at a level of differentiation at which one production line of the cell machinery is programmed to make these compounds. It is possible that an identifiable carcinogen or promoting agent may be involved in causing the fixation of diverse tumors at an "APUD level" or in activating one or more segments of DNA. This would seem unlikely from an agent causing a joint mutation, but perhaps a more selective biologic agent, such as a virus or oncogene, might be involved.

An exciting and puzzling cytologic phenomenon in diverse tumors is the oncocytoma-like replication of mitochondria which threatens to burst the cells. Double minute chromosomes also are found in diverse tumors, and in one of our colon carcinoma cell lines (with APUD products) they apparently replicate an oncogene. Although it may even be found that tumors making APUD products have a better prognosis and may respond differently than non-APUD tumors to chemotherapy, the entire APUD hypothesis requires refinement. Speculation, hypotheses, and even "proofs" are only halting steps toward understanding cancer, but they add zest to the search for the relief of fear, pain, and premature death from malignant disease.

GEORGE E. MOORE, MD, PhD
Director of Surgical Oncology
Denver General Hospital
Denver, CO 80204

Hepatitis A: common and costly

The paper by Hanrahan et al in this issue of the *Journal* is a reminder that hepatitis A remains an important problem in the United States. According to a recent report by the Centers for Disease Control (CDC),[1] viral hepatitis is (after gonorrhea) the second most frequently reported infectious disease in this country. Hepatitis A accounts for 45% of the total reports received by the CDC each year. Unlike gonorrhea, which usually responds to antibiotics, there is no specific treatment for hepatitis A, nor is there a vaccine *yet*. Both gonorrhea and hepatitis share the dubious distinction of causing an inordinately high morbidity but negligible mortality, and perhaps because of this they seldom make headlines. Nevertheless, as emphasized by the authors, both infections place a large burden on budgets allocated to infectious disease control in addition to generating other public and private health care costs. The epidemic described in this report cost nearly $40,000 in medical expenses and lost pay—all of which could have been averted had there been prompt reporting of the initial cases.

Recent estimates from the CDC suggest that the 25,000 to 30,000 cases of hepatitis A reported annually in the United States are the tip of a much larger iceberg conservatively estimated at 100,000 icteric cases yearly and many times that number if nonicteric, mild, or asymptomatic cases are included.[2] These numbers are staggering when compared to other infectious diseases reported nationally. The estimated cost is in the hundreds of millions of dollars.[3] Recent estimates for hepatitis B for both acute and chronic HBV-related diseases are put at $1 million a day.[4]

In the 1960s, Blumberg opened a medical Pandora's box with the discovery of the "Australia antigen," so named because it was first isolated from an Australian aboriginal.[5] Another force, Hope, was released from the box. In less than a generation, thanks to the research of Dane, Hilleman, Krugman, Purcell, Maynard, Szmuness, and others, an effective and safe vaccine was developed.

Immunization programs have achieved success in the prevention and control of polio, diphtheria, mumps, measles, and rubella. One surprising consequence of these efforts has been to refocus on the high incidence of hepatitis A among younger people. Hepatitis A might now qualify for listing in the "most common diseases of childhood." Food-borne outbreaks such as the authors describe contribute very little to overall annual case rates; the major contribution appears to be from myriad small outbreaks in day care centers and other closed settings for infants. Hepatitis A does not have a carrier state. However, transiently infectious infants, most of whom are asymptomatic, may cause adult cases and upon rare occasion outbreaks such as the one described by the authors.

A tissue culture vaccine developed by Merck, Sharp and Dohme is undergoing trials in chimpanzees. The New York State Department of Health has recently developed a recombinant DNA technique using vaccinia virus particles that may allow for the development of a variety of vaccines including another type of hepatitis A vaccine. If these vaccines prove successful, then the next generation of physicians may come to regard a rare case of hepatitis A in much the same way as present-day house staff are set astir by a single case of measles.

JOHN S. MARR, MD
Assistant Medical Director
Exxon Corporation
1251 Avenue of the Americas
New York, NY 10020

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Caution on synovial sarcoma

The value of the paper on synovial sarcoma by Rajpal, Moore, and Karakousis in this issue of the *Journal* lies not in disclosing new information, but in reinforcing existing impressions of synovial sarcoma. This tumor is highly aggressive as reflected in a 34.6% recurrence rate and a 77% rate of metastasis. The five-year survival of 43.5% as quoted is misleadingly optimistic and does not adequately reflect the natural history of this disease. Synovial sarcoma is known to metastasize late. A more accurate assessment of the aggressiveness of this tumor is to quote five-year disease-free survival rates. Clearly the majority of the 77% of patients who experienced metastasis will succumb to their disease as evidenced by their median survival of 14 months and five-year survival of 2.5%. Therefore the ten-year survival will drop dramatically from the figure of 43.5% quoted at five years.

The overall amputation rate of the extremity lesions was 46% with 55% in the lower extremity and 40% in the upper extremity. The authors contend that these rates may in fact be high and that with further advances in adjuvant treatment limb salvage procedures will increase in frequency. However, their results did not support this contention. Amputation in the lower extremity was almost exclusively used for distal lesions. They rationalized this by stating that wide margins are not achievable in lesions in the distal aspect of the extremity. They also claim that there is no significant correlation between surgical margins and subsequent recurrence. However, the recurrence rate for amputation was 12%; for wide local excision it was 33% and with simple excision it was 67%. Limb salvage attempts were therefore applied to proximal lesions that had a greater percentage of larger tumors (84% *v* 60%), were deep seated, and invariably represent IIB lesions which prove difficult to remove with wide or radical margins. Not unexpectedly the five-year survival rate for patients with distal lesions was 58.7% and for those with proximal lesions 12.8%. As such limb salvage was inappropriately applied to lesions at highest risk for recurrence and metastases. Attempts at limb salvage should be reserved for the selected patients in whom wide or radical margins can be achieved. I doubt this will represent 54% of cases as reported in this series.

The anticipated greater local control and decrease in metastasis with the use of adjuvant chemotherapy, radiation therapy, or both has not materialized in this series. Adjuvant modalities were predominantly used in combination with attempts at local excision of the tumor. As shown above, the survival rates are drastically different between the two population groups (amputation *v* local excision) indicating no significant advantage of adjuvant treatment in local control nor control of metastasis. Also, when chemotherapy or radiation or both were applied alone or in conjunction with surgery for known metastatic disease there was no apparent benefit.

FRANKLIN H. SIM, MD
Professor of Orthopedic Surgery
Mayo Clinic
Rochester, MN 55905

Diagnosis and management of synovial sarcoma

Although synovial sarcomas occur infrequently compared with cancers of the lung, intestine, and breast, they are not rare. And they strike the young.[1] Rajpal and his colleagues report a mean age of 33.6 years in their series reported in this issue of the *Journal*. These tumors occur most often in the extremities but also occur in other soft somatic tissues, including the head and neck. Treatment failures are frequent because sarcomas are prone to local recurrence and metastasis.[2,3] As illustrated in the report of Rajpal et al, and others,[1-3] patients may suffer the trauma of losing a limb in order to prevent the spread of tumor, only to die unexpectedly due to metastasis.

Early diagnosis of synovial sarcoma permits more effective treatment and a much higher survival rate. Thus, over 70% of patients treated for tumors smaller than 5 cm in diameter have survived five or more years, as compared with only 40% to 48% of patients treated for larger lesions.[2] A mass is often the only presenting symptom. The tumor need not be intimately associated with the synovial membrane of a joint. In fact, most synovial sarcomas bear no demonstrable relationship to joints.[3] Rather, they tend to arise in muscular septa, aponeuroses, tendons, tendon sheaths, and synovial bursae.[1,3] In 1954 King[4] and others, citing evidence from anatomic, embryologic, histologic, and histochemical studies, observed that these tumors of diverse anatomic origin showed similar morphology. For these reasons, Hajdu et al[1] have proposed that tendosynovial sarcoma might be a preferable name, encompassing the synovial sarcomas as commonly referred to, but also the less common epithelioid, clear cell, and chordoid sarcomas which show evidence of a common histogenesis.

Knowledge of the radiologic and pathologic characteristics, as reviewed by Berlow and Markarian in this issue of the *Journal*, is important in the diagnostic evaluation of the patient presenting with such a tumor. The ultimate diagnostic confirmation of synovial sarcoma requires the performance of a biopsy. Incisional biopsy is the technique of choice. It provides enough tumor tissue for histopathologic study and causes minimal contamination of the overlying normal tissues. The biopsy scar and tract need to be excised *en bloc* with the sarcoma during definitive surgical resection, leaving behind no microscopic residual. While a small, superficial tumor can be completely excised for pathologic study, excisional biopsy or enucleation of deep-seated sarcomas is not recommended because it results in spilling of sarcoma cells in multiple tissue planes so that complete eradication by surgery or other means may become difficult if not impossible.

Considerable advances have been made during the last decade in the treatment of soft tissue sarcomas. One or two decades ago, local tumor recurrences were common after surgical resection of synovial sarcomas, and amputation was frequently performed in the treatment of the primary or recurrent sarcoma.[1-3] Today, the limb can be preserved in most cases of malignant soft tissue tumors, including synovial sarcomas, that arise in the upper or lower extremity. These sarcomas tend to recur locally because of invisible, microscopic extensions of the tumor not recognized during resection and thus left behind. Deliberate wide excision of adjacent tissues such as by muscle group resection[5] can appreciably reduce the local recurrence rate, especially with tumors in fleshy parts of the limbs, but this often entails considerable loss of normal structures and limb function. Very good preservation of limb function and local tumor control have been accomplished in recent years by combining preoperative radiation therapy,[6] postoperative radiation therapy,[7] perioperative brachytherapy using tumor-bed implants of iridium-192 seeds,[8] or regional intra-arterial infusion of doxorubicin plus radiation[9] with carefully planned resection of these sarcomas. Very high radiation doses are required and great care must be exercised in the selection and management of patients subjected to such combined therapy in order to avoid serious treatment complications. There are limitations to all of these methods of treatment, and their relative merits for the treatment of sarcomas of a given anatomic location, size, or tissue type are matters of continuing study in several centers.

Adjuvant chemotherapy with doxorubicin or doxorubicin plus other chemotherapeutic agents has remarkably decreased the risk of death from metastatic disease in patients treated for soft tissue sarcoma in general, including synovial sarcoma, as shown by a prospective randomized study at the National Cancer Institute,[10] and in retrospective studies.[11]

The patient with a synovial sarcoma today, in contrast to one or two decades ago, has a reasonable chance of successful local tumor control, often with good preservation of limb or body function, and freedom from metastatic disease after a program of multidisciplinary therapy. However, much remains to be learned in this disease, for we still do not know what causes it, how it can be prevented, and why we fail to control some of these tumors but succeed in others.

MAN H. SHIU, MD
Associate Attending Surgeon
Memorial Sloan-Kettering Cancer Center
New York, NY 10021

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The CPC, revived

The decline of the autopsy as an instructional tool over the past decade resulted from increased difficulties with permission procedures and concerns over the time and effort required for its performance. Against the broader canvas of rapid and sophisticated chemical studies, more readily available tissue biopsies, and improved diagnostic imaging, the autopsy seemed to have less value than before.

More recently, however, many have expressed concern about this decline. It is now apparent that the newer technologies that permit the imaging of body parts and functions cannot provide all of the answers. This has produced renewed interest in the autopsy as a teaching and learning method, especially in difficult diagnostic cases.

The clinicopathologic conference (CPC) has clearly demonstrated its value, even in this era of sophisticated technology. Renewing an old tradition, the editors are pleased to present in this issue of the *Journal* the first of what will be a regular series of clinicopathologic conferences. It is our hope that these conferences will challenge the reader's clinical acumen through case presentations, and stimulate interest in the information presented by discussors and pathologists.

Major teaching institutions and hospitals throughout the East have generously responded to requests from us for assistance in this effort. We are extremely grateful to them and would welcome cooperation from other institutions as well. We encourage comments, criticisms, and suggestions aimed at enhancing the educational value of the CPC for student, clinician, and researcher alike.

JOHN T. FLYNN, MD
Consulting Editor

LETTERS TO THE EDITOR

Address correspondence to Editor, New York State Journal of Medicine, *420 Lakeville Road, Lake Success, NY 11042. Letters should be typed double-spaced and include the signature, academic degree, professional affiliation, and address of each author. Preference is given to letters not exceeding 450 words, and every effort will be made to assure prompt publication. All letters are personally acknowledged by the Editor.*

Stilbamidine: *tempus fugit*

TO THE EDITOR: The recent report of the occurrence of pulmonary blastomycosis in a patient in New York City[1] recalled a bit of medical history about the first use of the aromatic diamidines in the treatment of this fungus disease. In 1950, a specific form of therapy for North American blastomycosis did not exist and the hospital admission of an extremely ill patient with systemic disease created an urgent problem in treatment.

In 1948, Schoenbach and Greenspan[2] wrote an extensive review about the pharmacology, mode of action, and therapeutic potentialities of the aromatic diamidines. They recalled the use of these compounds in a number of diseases and stated that a clinical trial of the diamidines in the treatment of systemic or cutaneous fungus disease had not been reported.

Based on his knowledge of these drugs, Schoenbach suggested the use of the diamidines in the treatment of the patient with blastomycosis.[2] Such therapy was started in December 1950, with stilbamidine being given intravenously and propamidine being applied topically. The immediate therapeutic effects of these drugs was excellent.[3] Subsequently, three other patients were treated with similar good results.[4]

Later, other antimicrobial agents for the treatment of blastomycosis were discovered. Amphotericin B is universally regarded as the treatment of choice, with stilbamidine being reserved for the treatment of patients with chronic dermatologic disease. Ketoconazole is less toxic than amphotericin B, although amphotericin B still remains the preferred treatment for blastomycosis.

A comparison to the sulfonamides is most apt. They were the first effective chemotherapeutic agents to be employed systemically for the treatment of bacterial infections in man, and were followed by a great number of compounds efficacious against bacteria. So, too, the advent of amphotericin B has reduced the value of the diamidines in the treatment of blastomycosis, but the use of stilbamidine inaugurated a new era in the treatment of fungal disease.

JOSEPH M. MILLER, MD
Director of Medical Education
Provident Hospital
2600 Liberty Heights Ave.
Baltimore, MD 21215

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Thermography in the diagnosis of reflex sympathetic dystrophy

TO THE EDITOR: Reflex sympathetic dystrophy is a regional disorder of a limb characterized by burning pain with hypersensitivity of the skin to light touch, heat, or cold. Sometimes the skin is shiny and has vascular discoloration. Early diagnosis of this condition with clinical methods alone is difficult and often impossible. X-ray films and electrophysiologic studies have proved of no value. However, a new painless, safe method of diagnosis, namely, contact thermography, proved very helpful in making the diagnosis.

Among 128 patients referred for neurologic consultation because of unexplained pain in a limb, usually post-traumatic, I found regional increase or decrease of skin temperature at least 1.0°C in a nondermatomal region of the body which was also painful in 29 cases (23%). This permitted a diagnosis of reflex sympathetic dystrophy.

Recently, using the same method, Thomas Ravin, MD, of Colorado Springs, diagnosed 12 such cases. He was able to confirm impaired blood flow in his cases with radionuclide studies. All 12 of his cases were successfully treated, 7 with sympathetic blockade and 5 with active physical exercise.

In short, reflex sympathetic dystrophy is a painful vasomotor disorder of a limb which appears in a small percentage of cases following major or minor injury to a limb, myocardial infarct, hemiplegia, or without antecedent disorder. It can be diagnosed with contact thermography and responds to early treatment. If treated early, it can be treated successfully. The treatments are physical exercise, active physical use (despite temporarily increased pain), a short course of modest doses of cortisone, or a sympathetic block.

ARTHUR ECKER, MD
407 University Ave
Syracuse, NY 13210

Metabolic alkalosis

TO THE EDITOR: Spital and Chideckel (*NY State J Med* 1983;83:1058–1060) describe the occurrence of acute metabolic alkalosis following the relief of a urinary tract obstruction. In their discussion of the possible pathophysiologic mechanisms involved, the authors invoke the concept of a "contraction alkalosis." On the basis of recent experimental observations, this notion may be incorrect and outdated.

With the technique of *in vitro* perfusion of isolated nephron segments, the regulators of acid-base balance can be studied individually under controlled conditions that eliminate the interference of confounding variables such as serum potassium concentration, volume status, and hormones.[1] In the proximal tubule, which has been proposed as the locus of response in contraction alkalosis, studies indicate that addition or removal of peritubular protein from the solution bathing the proximal tubule segment does not alter bicarbonate reabsorption.[2] These findings, which have been verified with microperfusion and free-flow techniques,[3] suggest that peritubular protein per se, an index of the volume status of the individual, changes in arterial pCO_2 and serum potassium concentration are direct mediators of hydrogen ion secretion by the proximal tubule.[4] In distal nephron segments, the key regulator of acidification appears to be the serum aldosterone level, with contributions by the arterial pCO_2 and serum potassium concentrations.[5] When taken together these findings support the current notion that the volume status of an individual has no direct influence on renal acidification. The metabolic alkalosis that results in states of contraction of the actual or effective circulating blood volume is mediated by changes in the serum aldosterone concentration. Thus, the existence of "contraction alkalosis" as a distinct clinical entity is a misnomer. Disturbances of acid-base balance that result in metabolic alkalosis should be analyzed in terms of the factors that initiate the process and those that allow it to be perpetuated.[6]

In the patient described, the development of metabolic alkalosis was probably the result of depletion of the circulating blood volume and secondary hyperaldosteronism. This is supported by the marked negative fluid balance observed in the 24-hour period following relief of obstruction. This led to a significant urinary excretion of acid resulting in the paradoxical aciduria seen in metabolic alkalosis. Secondary factors contributing to the development of the metabolic alkalosis were hypokalemia and potassium depletion that were a result of the post-obstructive diuresis. An explanation of the phenomenon using these physiologic concepts avoids the oversimplification and confusion that arise when using the term "contraction alkalosis."

HOWARD TRACHTMAN, MD
Downstate Medical Center
Brooklyn, NY 11203

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In reply: Dr Trachtman suggests that the metabolic alkalosis we observed can be *fully* accounted for by renal acid excretion stimulated by secondary hyperaldosteronism. We disagree. As we pointed out, although it is likely that renal acid excretion contributed to the rise of the serum bicarbonate concentration, it is highly unlikely that it can fully account for the magnitude of the rise observed. We based this conclusion on the enormous rate of renal acid excretion which would have been required and the known effect of obstruction to interfere with renal acidification.[1] Furthermore, there was never any evidence of extracellular fluid volume (ECF) depletion to explain hyperaldosteronism—rather there was a return to normal of an expanded ECF. In addition, elevated aldosterone levels alone may not cause a rise in serum bicarbonate. Aldosterone secretion may actually fall in metabolic alkalosis generated by gastric drainage of hydrochloric acid—a state associated with contraction of the ECF.[2]

Dr Trachtman also implies that contraction alkalosis results from negative external hydrogen ion balance. This is not true. The concept of contraction alkalosis refers to metabolic alkalosis generated by contraction of the volume of distribution of a given amount of bicarbonate—it is independent of external hydrogen ion balance.[3] Thus, renal acidification is irrelevant. While this process is usually clinically insignificant, we resubmit that it is likely to have played a role in our patient.

Finally, we disagree with Dr Trachtman's attempt to discredit the role of volume status in renal acidification. While volume status may be a "confounding variable" in the research setting, and while it may act indirectly, it is often a significant factor in the intact organism.[4,5]

AARON SPITAL, MD
Rochester General Hospital
Rochester, NY 14621

ELLIOTT W. CHIDECKEL, MD
West Virginia University

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Digital babel

TO THE EDITOR: Many hospitals are planning to place information regarding inpatients into computer memory and supply terminals at nursing units for retrieval and other operations. This is a great idea whose time has come. The danger lies in the fact that each hospital may select a different system with the consequence that physicians who are on the staffs of several hospitals may be confronted with the need to learn and remember several complex systems in order to function. This potential for error and confusion has to be regarded as a serious problem unless some uniformity is imposed.

A. W. ZORGNIOTTI, MD
Professor of Clinical Urology
New York University Medical Center
School of Medicine
550 First Ave
New York, NY 10016

Disulfiram-like reaction to cefmenoxime

TO THE EDITOR: Cefmenoxime (AB-50912, Takeda-Abbott Laboratories) is an investigational third-generation cephalosporin with a broad spectrum of antimicrobial activity in vitro against gram-positive and gram-negative aerobic and anaerobic bacteria.[1,2] It is currently undergoing clinical evaluation.

Case report. A 23-year-old man with chronic osteomyelitis of the right leg underwent surgical debridement of the right tibia. Bone cultures yielded *Staphylococcus aureus* susceptible to cefmenoxime (minimum inhibitory concentration = 1 μg/mL). The patient had no history of penicillin or cephalosporin allergy and had normal renal function. After informed consent was obtained, a Hickman catheter was placed and the patient was instructed on self-administration of intravenous cefmenoxime in a dose of 2 g every six hours. After one week of inpatient therapy the patient was discharged to complete the course of the antimicrobial as an outpatient; no other medications were prescribed. On the first outpatient day the patient, who was seated, began to consume a 12-oz can of beer approximately 3½ to 4 hours after the last dose of cefmenoxime had been administered. Before 8 oz of the beer had been consumed, the patient noted bright red flushing of the face which progressed to involve the trunk and arms. Within minutes, the abrupt onset of a throbbing headache, palpitations, and anxiety were noted. Feeling uneasy, the patient stood up but experienced lightheadedness, dizziness, and blurring of vision. No gastrointestinal distress was noted. The symptoms improved after one-half hour and completely resolved in one hour. The next scheduled dose of cefmenoxime was administered without complication one hour after the episode. The patient was instructed not to consume alcohol and the treatment course was completed without further disulfiram-like reactions.

Discussion. In this case, the symptoms experienced were those typically described with disulfiram-like reactions: flushing, throbbing headache, blurring of vision, palpitations, lightheadedness, and dizziness. However, nausea and other common gastrointestinal manifestations were absent. As in most milder cases of disulfiram-like reactions, the symptoms started to subside in one-half hour and had fully resolved by one hour. No specific therapy other than bedrest during the episode was required.

Cefmenoxime is structurally related to cefamandole, cefoperazone, and moxalactam in possessing a methyltetrazolethiol side chain at the 3-position of the cephalosporin nucleus. Cefamandole,[3,4] cefoperazone,[5–7] and moxalactam[8,9] are cephalosporins that have been reported to cause disulfiram-like reactions in patients consuming alcohol containing products after pretreatment with these agents.

The mechanism of this reaction has been elucidated.[9] Methyltetrazolethiol, cefamandole, cefoperazone, and moxalactam were shown to inhibit acetaldehyde metabolism in laboratory animals. Exposing animals to alcohol after pretreatment with these agents resulted in accumulation of acetaldehyde, which had been implicated as the mediator of disulfiram-like reactions.[9] Cephalothin, cefazolin, cefoxitin, cephradine, and cefotaxime are cephalosporins that do not contain a methyltetrazolethiol side chain. They did not induce acetaldehyde accumulation. Since cefmenoxime contains the chemical moiety, methyltetrazolethiol, the occurrence of this adverse reaction was not unexpected.

BRUCE R. SMITH, Pharm D
JACK L. LeFROCK, MD
Division of Infectious Diseases and Clinical Microbiology
Hahnemann University
230 North Broad Street
Philadelphia, PA 19102

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Reliability of ACTH levels in Cushing's syndrome

TO THE EDITOR: A major review of Cushing's syndrome[1] emphasizes that ACTH levels differentiate between ACTH hypersecretion and autonomous hypersecretion of an adrenal tumor. We describe a patient whose ACTH levels measured by a large commercial laboratory were repeatedly unreliable.

Case report. A 30-year-old man was admitted to Coney Island Hospital in August 1981 with a history and physical examination typical of Cushing's syndrome. Morning and midnight serum cortisol levels, urinary 17-hydroxycorticosteroids (17-OHS), and urinary free cortisol were elevated and did not suppress with low-dose (2 mg/day) or high-dose (8 mg/day) dexamethasone. Values for 17-ketosteroids (17-KS) were normal. Computed tomography (CT) revealed a 5-cm left adrenal mass. Adrenal adenoma was diagnosed and surgery was planned. Blood for ACTH was drawn using chilled, heparinized, syringes and tubes, kept on ice, centrifuged, frozen immediately, and sent to a large national laboratory. The result was 82 pg/mL (normal morning range, 20 to 100 pg/mL). This is most consistent with pituitary Cushing's syndrome and not with adrenal tumor.[1,2].

Normal ACTH levels and absence of high dose dexamethasone suppression can occur in adrenal nodular hyperplasia[2,3] where unilateral masses have been seen on CT.[3,4] He was readmitted for eight days for very high dose dexamethasone suppression (32 mg/day) and a metyrapone test; dexamethasone did not suppress and 17-OHS levels decreased with metyrapone. Another carefully handled specimen was divided and sent to the original laboratory and to a second laboratory in California. The original laboratory again found a normal ACTH level (42 pg/mL), but at the second one the level was undetectable (<20 pg/mL). At surgery the left adrenal gland was replaced by a 5-cm adrenal adenoma. Six weeks later, the patient's morning cortisol was 5.1 μg/dL with an ACTH of 85 pg/mL (at the second laboratory).

Discussion. According to a review of Cushing's syndrome,[1] ACTH by radioimmunoassay is the best procedure for establishing pathogenesis, and pharmacologic manipulation of endogenous ACTH is unnecessary. The ACTH radioimmunoassay has traditionally been difficult for many reasons including low circulating levels, lability of ACTH, and difficulty obtaining sensitive, specific antibodies.[2,3] Nevertheless, many commercial laboratories perform this assay with questionable reliability. Using the recommended protocol[1] without dynamic testing or computed tomography, we would have concluded that our patient had a pituitary lesion based on normal ACTH levels. This could have resulted in inappropriate pituitary surgery. The spurious ACTH level resulted in eight additional hospital days and delayed definitive therapy for six weeks.

Therefore, in determining pathogenesis of Cushing's syndrome, a laboratory with a reliable ACTH radioimmunoassay is essential, and other confirmatory tests should be performed.

JOEL M. GOLDMAN, MD
HILARY C. BRYNILDSEN, MD
MARY F. WHEELER, MD
Division of Endocrinology
Coney Island Hospital
Brooklyn, New York 11235

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Abraham Flexner

TO THE EDITOR: In a recent essay comparing medical education, past and present, reference was made to the famous Flexner Report by the late "Abraham Flexner, MD" (sic) (*NY State J Med* 1983;83:1172). It is my recollection that the report was authored by a nonphysician. Perhaps that is the real lesson to be learned concerning our present state of affairs in medical education.

MARVIN GOLDSTEIN, MD
375 Hooker Ave
Poughkeepsie, NY 12603

Abraham Flexner

TO THE EDITOR: Your recent reprint of "Medical Education" by E. A. Vander Veer and the accompanying editorial review, "Medical Education—Then and Now" are welcomed (1983; 83:1170–1171). It is good for us to reflect on the thoughts and beliefs of former analysts and clinicians.

Flexner's report of 1910 deserves a reading by contemporary educators. It sometimes requires a certain distance from a discipline to gain an appropriate perspective. A lesson of Flexner's report is that we should listen to what others are saying today about medical education.

A slight error appears in the editorial which appends an MD after Abraham Flexner's name. He was not a physician, but an educator who spent his life analyzing educational programs.

ANTHONY C. MUSTALISH, MD
Chief, Emergency Services
Lenox Hill Hospital
New York, NY 10021

In reply: Dr Goldstein is correct in his recollection of Abraham Flexner. Flexner was an internationally respected educator and not a physician. However, he held two honorary MD degrees from the University of Berlin (1929) and the University of Brussels (1930). For this reason the initials MD sometimes appear after his name.

PASCAL JAMES IMPERATO, MD
Deputy Editor

Pneumomediastinum occurring in association with facial trauma

TO THE EDITOR: Pneumomediastinum occurring in association with facial trauma is an uncommon entity. Air in the mediastinum is of benign import, but may indicate an underlying serious injury such as perforation, laceration, or rupture of the larynx, trachea, bronchus, lung, esophagus, or other visceral organ. It may also be associated with relatively innocuous neck or facial trauma. It may be present as a complication of operative dental procedures, gunshot wounds of the maxillary sinus, fracture of the orbital floor, or fracture of the maxillary antrum.

A case of fracture of the lateral wall of orbit and inferolateral wall of maxillary sinus associated with pneumomediastinum is presented.

Case report. A 33-year-old man came to the emergency room following blunt trauma to the face. The patient complained of pain in the left eye, swelling of the neck, and change of voice.

Initial examination showed the patient to be in no acute distress. The periorbital tissue on the right and left sides showed swelling and ecchymosis, more severe on the left than on the right side of the face. Crepitus was heard in the area of the neck and over the right orbital area.

Initial x-rays included studies of the chest, neck, and orbits. Chest x-ray film demonstrated a pneumomediastinum. Lateral neck film showed subcutaneous emphysema and air in the retropharangeal space. Frontal view of the facial bones showed subcutaneous air in the scalp and right orbital fossa.

Barium swallow and computer-assisted tomography of the sinus, orbits, and neck were performed. The barium swallow test results were normal. The CT scan of sinus and orbits revealed fractures of the lateral wall of the orbit and inferolateral wall of maxillary sinus. CT scan of the neck showed air within the fascial planes.

The patient was admitted for observation and placed on antibiotic therapy.

Discussion. Extensive communication between the face, neck, and mediastinum occurs through fascial planes leading to pneumomediastinum from facial trauma. Pneumomediastinum may also occur secondary to rupture of trachea, bronchus, or esophagus within the mediastinum, rupture of interstitial tissue of lung, air in the retropharyngeal space, and air tracking through the fascial planes of the neck.

Trauma with fractures of the facial bones leads to air communication between the maxillary or ethmoid sinuses and the fascial planes of the neck, and hence the pneumomediastinum. Air in the mediastinum can indicate a serious penetrating injury. It may also represent a benign finding associated with relatively insignificant neck or fascial trauma, as in this case. Before pneumomediastinum is labelled as a benign finding other causes of pneumomediastinum should be ruled out. Treatment should be directed toward the cause of air leak.

KIRAN CHAWLA, MD
STEVEN STEINBAUM, MD
LESLIE L. ALEXANDER, MD
Department of Radiology
Queens Hospital Center
Jamaica, NY 11432

Cianchetti JA, Carboll GF: Traumatic pneumomediastinum resulting from facial trauma. *Ann Emerg Med* 1980; 9:218-221.

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Very late recurrences of cancer

TO THE EDITOR: Adler et al (*NY State J Med* 1983; 83:1037-1038) described the recurrence of a bronchiolar carcinoma 19 years after surgical excision. Nothing was mentioned in regard to emotions or life situation.

All physicians know, even though many forget at times, that cancer is a two-way process—a constant battle between the invasive force of the malignancy and the host's resistance, primarily the lymphocytes and phagocytes of the cellular immune defenses. These defenses are variable in their activity level. Kavetsky et al[1] and Balitsky et al[2] have suggested they are more active in the presence of a cerebral cortical state perhaps best described as alert, hopeful, and active. Similarly, "spontaneous" regressions of cancer seem related to major newly favorable life situations in reported instances in which the latter were inquired about.[3-5] Some examples are: reconciliation with a long-hated mother; love and marriage after renunciation; release from a highly dependent relationship; religious conversion; and powerful placebo effect from a medically questionable anticancer drug.

CHARLES WEINSTOCK, MD
903 Park Avenue
New York, NY 10021

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In reply: The issue raised by Dr Weinstock, namely, the relationship of life situation and emotions to progression or regression of cancer, has been the subject of speculation by a number of investigators. The information gleaned from our brief single case report would not add significantly to that literature. Other behavioral therapists have attempted to improve the prognosis of patients in regard to their tumors. Whether or not such interventions are helpful is not known. Nevertheless, as Dr Weinstock notes, attempts to promote host resistance to the development and progression of cancer deserve attention.

JACK J. ADLER, MD
Brookdale Hospital Medical Center
Brooklyn, NY 11212

CORRECTION

The title of a case report by Drs Cohen, Mitchell, and Marx (*NY State J Med* 1983; 83: 1060) contained a misprint. The correct title is, "Severe systemic reactions following administration of different uterotonic drugs."

An outbreak of hepatitis A linked to a food handler in a cafeteria

JOHN P. HANRAHAN, MD, KEVIN L. ZIMMERMAN, MARTIN H. TOLY, RALPH L. PROWDA, MD,
JOHN C. GRABAU, PHD, DALE L. MORSE, MD

ABSTRACT In November 1981 an outbreak of hepatitis A affected 37 patrons of a cafeteria in Onondaga County, New York. An epidemiologic investigation implicated cold sliced meat sandwiches served during lunch as the probable vehicle of transmission. Interviews and serologic evaluation of all cafeteria employees revealed only one employee with clinical illness and acute-phase (IgM) antibody to hepatitis A virus (HAV). This employee's duties in the cafeteria included the preparation of sliced meat sandwiches, implicating him as the probable index case and source of the outbreak. He sought medical care during his illness, but no preventive action was taken. This outbreak emphasizes the importance of prompt reporting of hepatitis A in food handlers and other situations where the risk of widespread transmission is substantial. It further supports the efficacy of immune globulin (IG) prophylaxis in preventing secondary cases.

(NY State J Med 1984; 84:10–13)

INTRODUCTION

Outbreaks of hepatitis A caused by improper handling of food have long been recognized. Although reporting of cases of hepatitis A to local health authorities is mandated by all states, large and potentially preventable outbreaks of heaptitis A continue to occur. In November 1981, an outbreak of hepatitis A occurred among 37 patrons of a food service establishment in Onondaga County, New York. This outbreak was caused by a food handler with hepatitis A. The outbreak demonstrates that prompt reporting and follow-up investigation of persons with hepatitis A in high-risk settings are required to prevent widespread disease transmission.

In November 1981, the Onondaga County Health Department received numerous reports of hepatitis A occurring in persons employed in one building (Building A) in downtown Syracuse. Building A was opened in 1975 and is the center of county government and administrative agencies, housing 4,000 employees. Cafeteria A, located in the basement of Building A, is open weekdays for breakfast and lunch. Fifteen full-time staff are employed by the cafeteria, each of whom is involved in many aspects of food preparation and service.

METHODS

Once the outbreak was recognized, a joint epidemiologic investigation was conducted by the Onondaga County and New York State Health Departments. This included identification, confirmation, and evaluation of persons with hepatitis A; comparison with a control population; review of environmental risk factors associated with the outbreak; and follow-up case investigations to detect secondary cases.

Case investigation. We interviewed all persons with symptoms of hepatitis A reported to the Onondaga County Health Department between October 1 and December 1, 1981. A standard questionnaire was used to determine symptoms associated with hepatitis, duration of illness, place of employment, household contacts, history of eating in Cafeteria A and other local food establishments, as well as meals and food items consumed in the cafeteria.

A case definition for hepatitis A was established for suspect cases. To be included, a person was required to have three or more symptoms compatible with hepatitis A (fever, weakness, nausea, vomiting, anorexia, dark urine, light stool) in addition to one of the following: jaundice; physician-verified diagnosis of hepatitis A; or serologic demonstration of antibody of the immunoglobulin M (IgM) class to hepatitis A virus (IgM anti-HAV). An outbreak-related case was defined as a case of hepatitis A in a person who had eaten in Cafeteria A at least once between October 1 and December 1, 1981, and who did not have any other obvious exposure to a person with infectious hepatitis.

Persons with hepatitis A were identified by several means: These included routine cases reporting to the Onondaga County and New York State Health Departments, a health alert issued by the county health department to all Building A employees urging prompt reporting of all cases to the county health department, and extensive press and mass media coverage of the outbreak.

Comparison with controls. Each case was asked to identify two well persons of approximately the same age (±5 years) and sex who worked in close proximity. Controls identified in this fashion were administered the same questionnaire as cases. This questionnaire sought information on the frequency of eating breakfast and lunch at Cafeteria A, as well as frequency of consuming all menu items served in the cafeteria. The two groups were then compared to examine differences in exposure histories.

Food service investigation. All Cafeteria A employees were interviewed to ascertain if they had a clinical illness compatible with hepatitis A during September or October 1981. All employees also had a serum specimen assayed for IgM antibodies to HAV, indicating a recent HAV infection.

Secondary case investigation. Six weeks after the end of the

From the Division of Field Services, Centers for Disease Control, located at State of New York Department of Health, Albany (Dr Hanrahan); the Onondaga County Health Department (Mr Zimmerman, Dr Prowda); and the Bureau of Communicable Disease Control, State of New York Department of Health, Albany (Mr Toly, Drs Grabau and Morse)

Address correspondence to Dr Hanrahan, Medical Epidemiologist Bureau of Communicable Disease Control, New York State Department of Health, Room 651, Corning II Tower Bldg, Empire State Plaza, Albany, NY 12237.

Food Consumption Histories Associated with Hepatitis, Cafeteria A, Onondaga, County, NY

Meal or Food Item	Ate Specific Food/Meal				Did Not Eat Specific Food/Meal				
	Ill (Case)	Not Ill (Control)	Total	% Ill	Ill (Case)	Not Ill (Control)	Total	% Ill	χ^2 P Value
Lunch	28	32	60	47	9	28	37	24	<.05
Sliced cold meat sandwiches	21	16	37	57	16	44	60	27	<.01
Other cold sandwiches	15	16	31	49	22	44	66	33	NS
Cold drinks	20	19	39	51	17	41	58	29	<.05

outbreak, all persons with hepatitis A were again interviewed in order to ascertain secondary attack rates among their close contacts. Information related to prophylactic administration of immune globulin (IG), time between the onset of symptoms and IG administration to household members, home food preparation history of cases, and the occurrence of clinical hepatitis A among household contacts of cases was determined.

RESULTS

Between October 1 and December 1, 1981, 42 cases of hepatitis A were reported to the Onondaga County Health Department. Of these, 37 were patrons of Cafeteria A and included as outbreak-associated cases. The epidemic curve shows a peak occurrence of cases during the period November 4 through 20, 1981 (Fig 1). The index case had symptoms beginning on October 16, more than two weeks earlier than the next outbreak-related case. This person was a food-service employee in Cafeteria A.

The clinical illness occurring in the 37 patrons was typical of hepatitis A. Symptoms of dark urine, light-colored stool, fatigue, and anorexia were present in more than 90% of the ill persons, while noticeable jaundice or scleral icterus, nausea, abdominal discomfort, and fever were present in more than 80%. Of 30 persons reporting fever, 18 had taken their temperatures, and their highest ranged from 37.4°C to 39.6°C (99°F to 103°F), with a median of 38.8°C (102°F). All but one person had seen a physician for the illness, and six (16%) were hospitalized. Hospital stays ranged from one to 15 days (mean 6.3 days). All ill persons recovered.

The 37 cafeteria patrons with hepatitis A ranged in age from 23 to 57 years (mean 38.6 years); 16 (43%) were male and 21 (57%) were female. The control population of 60 persons ranged from 21 to 62 years of age, with a mean of 35.1 years; 23 (38%) were male, and 27 (62%) were female. Twenty-four (65%) of the outbreak-related cases were employed in Building A, compared with 39 (65%) of the controls. Differences in exposure histories for cases and controls are depicted in the Table. Persons who contracted the disease were significantly more likely than controls to have eaten lunch in Cafeteria A at least once between October 1 and December 1, 1981 ($P < .05$). Both groups ate breakfast in Cafeteria A with the same frequency. Additionally, persons with hepatitis A ate lunch at the cafeteria with greater frequency than controls, but this difference did not attain statistical significance. Of the 17 food items included in the questionnaire, only two were associated with illness. Consumption of cold sliced meat sandwiches ($P < .01$) and the frequency of consuming them ($P < .001$) were both highly associated with illness. Drinking of cold beverages was also associated with illness ($P < .05$), but a dose-response relationship was not seen. Consumption of any cold sandwiches other than sliced meat sandwiches was not associated with illness, nor was any other exposure included on the questionnaire.

Nine (24%) of the 37 ill patrons had eaten at Cafeteria A on only one occasion during the suspect time period. All nine had eaten lunch at Cafeteria A on October 14, 15, 16, or 19, 1981. The cafeteria was closed for the weekend on October 17 and 18. These nine persons with single exposures allow for calculation of an incubation period for the outbreak-related cases. Time between exposure and symptom onset for these nine patrons ranged from 22 to 34 days, with a median of 26 days (Fig 2).

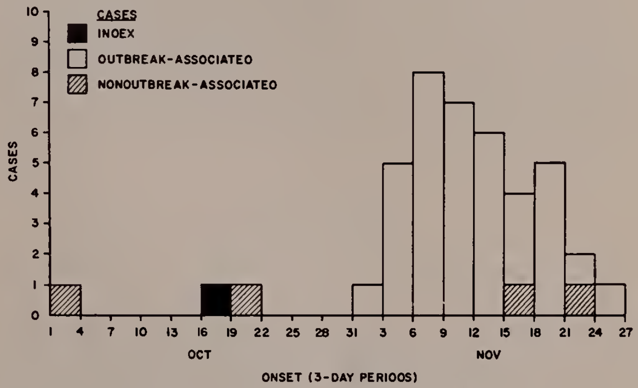

FIGURE 1. Hepatitis A, by date of onset, Onondaga County, New York, October–November 1981.

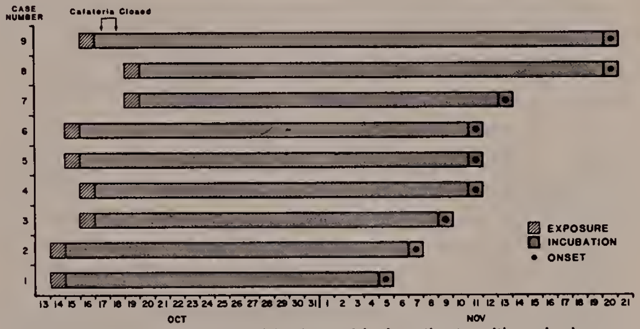

FIGURE 2. Incubation period for hepatitis A patients with a single exposure, Onondaga County, New York, 1981.

All 15 cafeteria employees were interviewed and questioned in depth to ascertain if any had a clinical or subclinical illness consistent with infectious hepatitis since September 15, 1981. Only one individual had such symptoms, a 22-year-old man who became ill with nonspecific symptoms on October 16. Severe weakness, lethargy, and jaundice caused him to seek medical attention at a hospital emergency room on October 21, 1981. At this time a clinical diagnosis of hepatitis A was established, but this finding was not reported to the health department, and the employee continued to work in the cafeteria. Like all of the cafeteria employees, he had varied duties, but throughout October he sliced meats, prepared cold-meat sandwiches, and prepared salads used in making sandwiches (eg, egg salad, tuna, etc.). He worked principally at the steam table during the busy lunch hours and occasionally made eggs or toast during the breakfast hours. He had no specific duties related to cold drinks or ice.

All 15 employees had serum samples taken November 24, 1981, to test for recent evidence of HAV infection. Five (33%) had anti-HAV antibodies of the immunoglobulin G (IgG) class, but only the index case had immunoglobulins of the IgM class against HAV, suggesting a recent infection. No other cafeteria employees developed clinical or subclinical symptoms consistent with hepatitis A.

Patrons with hepatitis A were interviewed a second time in late

January 1982 to determine the duration and severity of their illness and to identify secondary cases among their household contacts. Duration of symptoms for cases ranged from 11 to 80 days, with a mean of 33.8 days (median 28.5 days). Of 34 ill persons contacted during a follow-up interview, 32 had missed time from work due to hepatitis A. The time missed ranged from five days to more than ten weeks. Mean length of time missed was 20.0 work days, (median 16.5 work days).

Of the 37 primary cases, 31 had a total of 73 household contacts; six had none. Twenty-three (74.2%) of these 31 patrons with hepatitis A prepared some or most of the meals for these contacts. Sixty-six (90.4%) of 73 secondary contacts received exposure prophylaxis with IG (0.02 ml/kg). Timing of prophylaxis ranged from one to 42 days after primary cases developed symptoms, with a mean of 12.3 days. Among the 73 household contacts of primary cases, no clinically apparent secondary cases occurred. However, IgM anti-HAV serologic assays were not performed on follow-up evaluation of these 73 contacts, so that subclinical or asymptomatic HAV infection cannot be excluded.

DISCUSSION

This investigation identified hepatitis A among 37 patrons and one employee of a small cafeteria. The outbreak was typical of a common-source epidemic, with a single wave of illness that was statistically associated with eating lunch in the cafeteria, specifically with eating cold sliced meat sandwiches. One cafeteria employee had well-documented evidence of HAV infection (clinical symptoms and IgM antibody to HAV). Both the timing of his illness and his duties in the cafeteria implicated him as the index case in this outbreak.

The food associated with this outbreak, cold sliced meat sandwiches, is typical of previous food-borne common-source outbreaks of hepatitis A.[1,2] Implicated foods are almost invariably not cooked or are handled by human hands subsequent to cooking.[3] Although cold beverages were also significantly associated with illness, it is probable that this was a confounding rather than real association. Several lines of evidence point to this conclusion. First, the person identified as the index case had no specific duties related to cold drinks or ice. Second, of the 21 cases who consumed cold drinks, 14 (67%) had also eaten sliced meat sandwiches. Finally, a regression analysis of cold drink consumption controlling for consumption of sliced meat sandwiches demonstrated no significant association between cold drinks and illness.

The nine cases with a single exposure provide evidence for a period of at least six days (October 14 through 19) during which food was contaminated with HAV. This is consistent with experimental evidence of human fecal shedding of HAV for a period of seven to 11 days,[4] occurring as early as ten days before peak transaminase elevation and as late as the day of peak elevation.[5] This six-day period also concurs with epidemiologic evidence from previous food-borne outbreaks, where contamination spanned up to two weeks.[1,6] Other food-borne outbreak investigations have suggested the time of peak HAV shedding (and greatest risk of food contamination) may be limited to several days.[7] However, exposure risk in a food-borne outbreak may be longer, as many foods contaminated during preparation are served over an extended time period. Survival of HAV has been documented in refrigerated foods or foods kept at room temperature over a period of several days[3] and in dried feces stored for one month.[8]

None of the cafeteria employees other than the index case had serologic evidence of recent HAV infection (IgM anti-HAV) when tested one month after clinical illness in the index case. This suggested that other susceptible cafeteria employees had not been subclinically infected by their co-worker.

It has long been recognized that prophylactic administration of IG to exposed individuals prevents or attenuates HAV infections.[9,10] It is generally agreed that the protective efficacy of IG is greatest when administered soon after the time of exposure. Administration after onset of symptoms does not diminish the severity or duration of clinical illness. Recent guidelines suggest that it is of limited or no value and is not recommended if more than two weeks have elapsed from the time of exposure.[11] It is noteworthy that none of 73 household contacts of primary cases contracted clinically apparent hepatitis A, despite the fact that 74% of the primary cases prepared meals for these contacts. Sixty-six (90.4%) household contacts of primary cases of hepatitis A received IG prophylaxis, which was administered a mean of 12.3 days following onset of symptoms in primary cases. Since peak viral shedding precedes clinical symptoms by several days, it is probable that most cases received prophylaxis more than two weeks after their potential exposure. The absence of secondary cases, then, implies that few if any household contacts had sufficient exposure to contract hepatitis, that most contacts were already immune, or that IG prophylaxis may be effective in stemming disease even if administered somewhat later than two weeks after exposure.

Several studies have documented that IG administration to household contacts of hepatitis A cases reduces their risk of developing clinical HAV infection from about 6%–20% to 1%–3%.[12–14] Most household contacts in these studies who developed clinical HAV infection despite IG prophylaxis received IG therapy late in the incubation period, usually within ten days of symptom onset. These studies suggest that the prophylactic efficacy of IG may extend into the third week of the incubation period of hepatitis A. This possibility is further supported by studies demonstrating that different lots of IG afford various degrees of protection from HAV infection.[15]

Immune globulin is not routinely recommended for patrons of a food service establishment where a food handler with hepatitis A is identified, because food-borne outbreaks rarely result from the occurrence of hepatitis A in a food handler.[16] However, large-scale IG prophylaxis is justified when an infected person handles foods that are not cooked or handles cooked foods before they are eaten, when the food handler's hygienic practices are in question, and when IG prophylaxis can be administered to patrons at risk within two weeks of exposure.[11] Had the index case in this outbreak been promptly reported and confirmed (IgM anti-HAV), IG prophylaxis would have been indicated for certain Cafeteria A patrons at high risk of exposure.

A conservative estimate of the monetary cost of this outbreak, based only upon hospitalization costs and time missed from employment, would approach $40,000. This outbreak again demonstrates the crucial nature of prompt reporting of hepatitis A cases in food handlers and in other situations where the risk of widespread transmission is great.

Acknowledgements. The authors thank W. Rand, A. Chillemi, and J. Harris, MD, of the Onondaga County Health Department, and Donna Shadick and Diana Melewski of the Bureau of Communicable Disease Control, New York State Department of Health. We also thank Lorraine Good and John Andrews, MD, of the Division of Field Services, Epidemiology Program Office, Centers for Disease Control, for reviewing the manuscript.

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Deprenyl in the treatment of Parkinson's disease

A specific type B monoamine oxidase inhibitor

ABRAHAM N. LIEBERMAN, MD, GOVINDAN GOPINATHAN, MD, ANDREAS NEOPHYTIDES, MD, EMILE HIESIGER, MD, JEFFREY NELSON, MD, RUSSELL WALKER, MD, ALBERT GOODGOLD, MD

ABSTRACT Deprenyl (Jumex) is a specific inhibitor of type B monoamine oxidase (MAO). Unlike inhibition of type A MAO, type B MAO inhibition does not result in hypertensive crises after dietary indiscretion. Inhibition of MAO B results in increased concentration of dopamine at the receptors in the corpus striatum. Deprenyl was administered to 40 patients with Parkinson's disease who were no longer satisfactorily responding to levodopa (alone or combined with a decarboxylase inhibitor). The addition of deprenyl at a mean daily dose of 9.0 mg (range, 2.5 to 20 mg) resulted among the group as a whole in a significant reduction in disability. Individually, 19 of the 40 patients improved. Deprenyl was also effective in reducing one type of diurnal fluctuation in performance, end-of-dose deterioration or "wearing off" phenomenon. Deprenyl was not effective in reducing another type of diurnal oscillation in performance, the "on-off" phenomena. The addition of deprenyl permitted a 6.5% reduction in the dose of levodopa. Adverse effects related to the administration of deprenyl were those usually associated with "dopaminergic excess"—mental changes, dyskinesias, nausea—and were reversible upon stopping the drug. Deprenyl is a useful adjuvant in the treatment of Parkinson's disease.

(NY State J Med 1984; 84:13–16)

INTRODUCTION

Although most patients with Parkinson's disease in time improve on a regimen of levodopa, the response diminishes and is often associated with more disability than before initiation of treatment.[1] The worsening parkinsonism is frequently accompanied by diurnal oscillations in performance: end-of-dose deterioration or "wearing off" or "on-off" phenomena, and dyskinesias (choreoathetosis or dystonic posturing or both).[2] End-of-dose deterioration or "wearing off" refers to the gradual waning of the benefit from a given dose of levodopa that occurs two to four hours after the dose with an "off" period lasting until the next dose. "On-off" refers to the abrupt loss of effectiveness of a dose of levodopa that is not related to the timing of the medication, with an "off" period lasting minutes to hours followed by an abrupt return of effectiveness, an "on" period. Superimposed on "wearing off" and "on-off" phenomena are akinetic freezing spells with falls: episodes of momentary (seconds to minutes) inability to move"freezing") with loss of balance. In addition to motor deficits, depression occurs in up to 50% of patients[3] and dementia in up to 30%.[4]

The motor deficit in Parkinson's disease has been related to a deficiency in striatal dopamine resulting from the degeneration of the dopamine-producing neurons that arise in the substantia nigra and project to the striatum. Therapy with levodopa initially overcomes this deficiency because the remaining nigrostriatal cells are still able to synthesize dopamine in sufficient quantities to stimulate the dopamine

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From the Department of Neurology, New York University School of Medicine (Drs Lieberman, Gopinathan, Neophytides, Nelson, Goodgold) and the Department of Neurology, Sloan-Kettering Institute—Memorial Hospital (Drs Hiesiger, Walker), New York City

Address correspondence to Dr Lieberman, Professor, Department of Neurology, New York University School of Medicine, 530 First Ave NB 7W15, New York, NY 10016.

receptors.[5] However, in patients with advanced disease the degeneration of the nigrostriatal cells may proceed to the point where the remaining neurons are incapable of synthesizing dopamine in sufficient quantities to stimulate the receptors. While compensation for this may also occur, in part through the development of supersensitivity of the postsynaptic striatal receptors,[6] and in part through the ability of striatal intraneurons to convert dopa to dopamine,[7] in time these mechanisms also fail. While the progressive degeneration of the nigrostriatal neurons is responsible in large part for the increased disability, symptoms such as dyskinesias, "wearing off," and "on-off" effects may be more a consequence of chronic levodopa therapy with accumulation of toxic metabolites and receptor desensitization than of disease progression.[2,8] The episodic freezing spells and falls seen in these patients may have a still different mechanism, ie, they may represent involvement of nondopaminergic systems. Finally, the development of depression or dementia reflects involvement of nonmotor subcortical and cortical systems.

One approach to treating these patients is to potentiate the effects of dopamine by using drugs that delay its breakdown. Dopamine is catabolized by circulating catechol-O-methyl transferase and by intraneuronal monoamine oxidase (MAO). As MAO is not depleted in patients with Parkinson's disease, the administration of levodopa and a MAO inhibitor leads to increased striatal dopamine. Several early investigators combined levodopa with a MAO inhibitor, but the combination often resulted in hypertensive crises. Although these crises usually could be circumvented by combining levodopa first with a peripheral decarboxylase inhibitor (carbidopa, benserazide) and then with a MAO inhibitor, nonetheless, physicians remained reluctant to combine the drugs. It subsequently has been shown that there are two forms of MAO: A and B. Monoamine oxidase A is specialized for binding and metabolizing amines if they are attached to a 5-hydroxy-indole ring: serotonin, tyramine. Monoamine oxidase B is specialized for binding and metabolizing amines attached to a phenol ring: dopamine, norepinephrine. Intestinal MAO A controls the blood levels of the pressor amines in foodstuffs and blood vessels; MAO A protects the various organs from the toxic effects of these circulating amines. Inhibition of MAO A results in the pressor amines of foodstuffs gaining ready access into the circulation and the body organs. As an average meal of certain foods, especially some cheeses, contains enough tyramine to provoke a marked pressor response, it was soon realized that ingestion of these foods by patients while they were on MAO inhibitors was responsible for the hypertensive crises: the "cheese effect." In contrast to MAO A, which is mainly found outside the central nervous system (CNS), MAO B is mainly found inside the CNS, especially in the striatum. The MAO inhibitors that were available during the early studies with levodopa and the only ones that are still available for the treatment of depression in the United States are of the nonselective variety that inhibit both MAO A and B. An important advance was the development of MAO inhibitors that are selective for one or the other form of the enzyme. Deprenyl is a selective inhibitor of MAO B while clorgyline is a selective inhibitor of MAO A.[9-12] The administration of deprenyl in doses of 10 mg per day results in inhibition of MAO B without inhibition of MAO A, and thus avoids the pressor responses that occur with dietary indiscretion.[12]

METHODS

Forty patients with advanced Parkinson's disease who were no longer satisfactorily responding to levodopa participated. There were 12 women and 28 men. The mean age of the patients was 64.6 years (range, 41 to 82 years). The mean duration of their disease was 8.1 years (range, 2 to 20 years). All 40 patients had been treated with levodopa alone or combined with carbidopa as Sinemet. Mean duration of treatment was 7.0 years (range, 1 month to 14 years). Thirty-six of the 40 patients (90%) had improved on levodopa. However, in time, all of the patients had worsened and 20 (50%) were worse than they had been before beginning levodopa. Thirty of the patients (75%) were exhibiting "wearing off" phenomena, while eight of the 30 were also exhibiting "on-off" phenomena. Twenty patients (50%) had dyskinesias. Thirteen patients (33%) had freezing spells or falls. Fifteen patients (38%) were depressed, and 11 patients (28%) had a dementia. Nine of the depressed patients had been treated with tricyclic antidepressants and three were still on these drugs. Tricyclic antidepressants were discontinued in two patients and continued in one.

Prior to beginning deprenyl, a variety of other treatments were used. Ten patients (25%) underwent drug holidays in which levodopa was stopped for one or two weeks and then restarted in an attempt to restore the drug's efficacy. Four patients benefitted from the holiday, but the benefit was of short duration. Seventeen patients (43%) were treated with dopamine agonists: drugs acting directly on the receptors, including bromocriptine,[13] lisuride,[14] and pergolide.[15] However, in time, either the response to the agonists diminished or adverse effects occurred. Bromocriptine (one patient) and lisuride (three patients) were continued unchanged. Twelve patients had been treated with benserazide (another decarboxylase inhibitor) combined with levodopa as Madopar and three continued on this agent. All of the patients had been treated with amantadine and anticholinergic drugs and ten continued on amantadine and five on anticholinergic drugs.

Patients were assessed weekly the first month, and then monthly or bimonthly by a neurologist who was unaware of the patients' medications. The neurologist evaluated the cardinal signs of Parkinson's disease: rigidity, tremor, bradykinesia, postural stability, and gait using the NYU Disability Scale.[16] Each of the cardinal signs is given a weighted value. The total disability is the sum of the scores for each of the cardinal signs. On this scale for total disability, "O" represents no involvement, and "100%" represents maximum involvement. Patients were also staged on the scale of Hoehn and Yahr.[17] "Wearing off" and "on-off" phenomena were evaluated as previously described.[16] All scores were reported in "on" periods. Blood pressure was evaluated at each visit. Laboratory evaluation included hemogram, tests of liver and renal function, and urinalysis. Depression was evaluated by using a modified version of the Multiple Affect Adjective Check List (MAACL), a 132-item list filled out by the patient. Informed consent was obtained from all the patients or their spouses. The patients were aware of the medication they were receiving; placebos were not introduced.

Deprenyl was begun at 5 mg once a day and after a week was increased to the maximum 10 mg a day in two divided doses. Levodopa alone or combined with carbidopa or benserazide was initially unchanged, but later, in some patients, because of additive adverse effects (mental changes, dyskinesias), levodopa was decreased.

RESULTS

The addition of deprenyl to levodopa in 39 patients resulted in a significant improvement for the group as a whole in total score (NYU scale) and stage. In one patient, who in the past had been unable to tolerate levodopa, deprenyl combined with an anticholinergic drug resulted in improvement. The mean dose of deprenyl was 9.0 mg/day,

TABLE I. Results of Deprenyl Treatment in 40 Patients

	Mean Dose Deprenyl, mg (Range)	Mean Dose Levodopa, mg Sinemet (Range)	Score, NYU Scale	Stage
Before	0	930	37.9	3.4
		(0–1,500)	(± 3.2 SEM)	(± 0.1)
After	9.0	870	29.3	2.9
	(2.5–10)	(0–1,500)	(± 3.2)	(± 0.1)
Change		−6.5%	−8.6%	−14%
			$P \leq .01$	$P \leq .01$

TABLE II. Results of Deprenyl Treatment in 19 Responding Patients

	Mean Dose Deprenyl, mg (Range)	Mean Dose Levodopa, mg Sinemet (Range)	Score, NYU Scale	Stage
Before	0	925	43.1	3.6
		(0–1,500)	(± 3.0)	(± 0.1)
After	10	855	25.8	2.6
	(5–20)	(0–1,500)	(± 3.3)	(± 0.1)
Change		−7.5%	−40%	−28%
			$P < .001$	$P < .001$

and the dose of levodopa (in Sinemet) was reduced by 6.5% (Table I). One patient, on her own, increased the dose of deprenyl to 20 mg per day. Nineteen of the 40 patients (48%) improved at least one stage. The total scores and stages for these 19 patients are listed in Table II. Nineteen of the 30 patients (63%) with "wearing off" phenomena noted a decrease in this type of oscillation, while none of the eight patients who also experienced "on-off" phenomena noted a decrease in this type of oscillation. Two of the 13 patients with freezing spells or falls noted a decrease in the spells or in the number of falls. Mood improved in one of the 15 depressed patients.

Adverse effects were those associated with dopaminergic excess: Seven patients, including five with an organic mental syndrome, experienced confusion associated with personality or behavioral changes, delusions, or hallucinations. In all of these patients, deprenyl had to be stopped. Two patients experienced persistent nausea, and in both deprenyl had to be stopped. Five patients experienced more dyskinesias, and in one of them deprenyl was stopped. Two patients experienced gastrointestinal (GI) bleeding while on deprenyl. One patient with no prior history of GI bleeding developed melena after being on deprenyl for several months. An extensive evaluation revealed no source of the bleeding. The second patient had a past history of a duodenal ulcer. After being on deprenyl for several months, her ulcer perforated. There are no previous reports of GI bleeding on deprenyl. We can postulate no mechanism to explain the relationship. We believe that the bleeding and the use of deprenyl were unrelated in both instances; however, prudence induced us to discontinue the experimental drug. Deprenyl was discontinued in 13 patients (32.5%) because of adverse effects. All of the adverse effects disappeared within several days of stopping deprenyl. Deprenyl was discontinued in seven patients (17.5%) because of a lack of effect, and in one patient because of a declining effect. Deprenyl was discontinued in one patient who during the course of the study was discovered to be suffering from metastatic carcinoma. In all of the patients, there were no abnormalities in any of the laboratory tests that could be related to deprenyl.

The mean daily dose of deprenyl was 9.0 mg (range, 3 to 10 mg). The mean daily dose of levodopa in Sinemet was reduced by 6.5% from 930 mg (range, 0 to 1,500 mg) to 870 mg (range, 0 to 1,500 mg). The mean duration of the study was 5.0 months (range, 1 week to 22 months).

DISCUSSION

Deprenyl is an effective drug in many patients with advanced Parkinson's disease who are no longer satisfactorily responding to levodopa including patients with end-of-dose deterioration or "wearing off" phenomena. Our study is thus in agreement with those of others in which half of at least 500 patients improved when deprenyl was added to levodopa.[18-24] Deprenyl was discontinued in 22 of our 40 patients (55%) with advanced disease because of adverse effects or lack of efficacy. Nonetheless, we feel that deprenyl is useful because of the paucity of treatments available for patients with advanced disease. As deprenyl is thought by most investigators to act largely by inhibiting the catabolism of dopamine, deprenyl may be even more effective among patients with less advanced disease whose endogenous dopamine stores are relatively intact. Indeed, it has been postulated that through preserving these endogenous dopamine stores, deprenyl may prolong the period of time in which levodopa remains effective ("levodopa honeymoon").[18] There is some controversy regarding deprenyl's mode of action in Parkinson's disease. As noted above, the most widely accepted theory relates deprenyl's effect in

Parkinson's disease to the drug's ability to augment striatal dopamine. Supporting this theory are the observations that the features that improve the most are those that are largely under dopaminergic control, and the most frequent adverse effects are those associated with dopaminergic excess: mental changes, dyskinesias, and nausea. Moreover, the administration of deprenyl permits a reduction in the dose of levodopa (up to 25% in some studies), frequently while prolonging its activity (ie, lessening the "wearing off" effect). Deprenyl may augment the activity of striatal dopamine in one or several ways: (1) by inhibiting striatal mitochondrial MAO resulting in an increase in the intraneuronal pools of dopamine; (2) by blocking the reuptake of extraneuronal dopamine resulting in increased dopamine activity at the postsynaptic receptors; and (3) by inhibiting the presynaptic receptors on the cell bodies of the nigrostriatal neurons, the "autoreceptors," thus preventing stimulation of these autoreceptors by dopamine. As stimulation of the autoreceptors by dopamine results in "feedback" inhibition with decreased firing of the nigrostriatal neurons, deprenyl, by blocking this feedback inhibition, allows these neurons to continue firing.

A second theory relates deprenyl's efficacy in Parkinson's disease to the drug's conversion in the body to methamphetamine and amphetamine.[25] These two metabolites of deprenyl are believed to augment the activity of endogenous serotonin, norepinephrine, acetylcholine, substance P, and certain neuropeptides which in turn have an effect in Parkinson's disease. While this theory may explain some of activity in the disease, it is unlikely to be responsible for most of it. Thus, deprenyl has a greater effect in Parkinson's disease than amphetamine itself, and the effects of deprenyl are related more to the dopaminergic than to the serotonergic, noradrenergic, or cholinergic systems.[24]

A third theory relates deprenyl's efficacy solely to the drug's antidepressant effect. While deprenyl does have an antidepressant effect, this is less than its effect against Parkinson's disease. This contrasts with the activity of the tricyclic antidepressants, in which the antidepressant effect is greater than the effect against Parkinson's disease.

We believe that in addition to augmenting the activity of dopamine by preventing its catabolism, deprenyl and a lower dose of levodopa is more beneficial than a higher dose of levodopa (without deprenyl) because the lower dose of levodopa results in an increase in intracerebral dopamine similar to the higher dose but with the formation of 3-0-methoxydopa (30MD). The combination of increased intracerebral dopamine and decreased 30MD may be beneficial because recent evidence suggests that 30MD itself lowers intracerebral dopamine and thus negates much of the benefit of a higher dose of levodopa.[25]

Acknowledgments. The authors wish to thank Kathleen Faridazar, MD, and Ruth Schwartz, RN, for their help in monitoring the study; Professor J. Knoll, Department of Pharmacology, Semmelweis University of Medicine, Budapest, Hungary; Richard Berczeller, MD, New York, New York; Mr Gabor Farago, President, Medimpex Northamerica, Inc., New York, New York; Dr Zoltan Meszaros, Director of Scientific Research, Chinoin Pharmaceutical Works, Budapest, Hungary; and Dr E. Schwarczman, Manager, Medimpex, Budapest, Hungary for their help in obtaining deprenyl.

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Synovial sarcoma

A review of treatment and survival in 52 patients

SANJEEV RAJPAL, MD, ROBERT H. MOORE, MD, CONSTANTINE P. KARAKOUSIS, MD

ABSTRACT Fifty-two patients with synovial sarcoma were reviewed. This tumor occurred more frequently in the lower extremity, usually presenting as a soft tissue swelling. Surgical excision was the primary modality of treatment, usually in the form of amputation for tumors involving the distal extremity and wide surgical excision for tumors in the proximal extremity and trunk. Local recurrence was observed in 18 patients; the most effective treatment was surgical resection. Forty patients manifested metastases, predominantly in the lungs. Surgical resection of metastases in 19 patients, usually with chemotherapy, achieved a median survival of 19.5 months, whereas chemotherapy alone in 17 patients resulted in a median survival of 9.5 months. The overall median survival from initial diagnosis was 41.5 months, the five-year survival 43.5%, and the five-year disease-free survival 21.15%. Factors significantly affecting survival were tumor size and anatomic location of the primary tumor.

(NY State J Med 1984; 84:17–19)

INTRODUCTION

Synovial sarcomas have histologic features characteristic of synovial tissue and arise from synovial tissue near joints, tendons, and bursae.[1] Soft tissue sarcomas are infrequent, constituting only about 1% of all malignant tumors.[1] They are often dealt with as a group, although they behave differently according to their histology.

In the following review, the features of synovial sarcomas are examined in relation to prognosis and treatment.

PATIENTS AND METHODS

Fifty-two patients with histologically confirmed synovial sarcoma, seen at Roswell Park Memorial Institute (RPMI) in the period 1967 through 1977, were reviewed. Statistical methods used were the standardized life table method and chi-square. The mean age of the patients was 33.6 years with a range of 11 to 80 years.

There were 35 male and 17 female patients; 49 patients were white, two black, and one Oriental. The initial presentation of the tumor was usually swelling (46 patients, 88.5%), or local pain (26 patients, 30%), or both.

The most common site (67.3%) of the primary tumor was the lower extremity (Table I). Among patients with accurately known diameter of tumor the majority (70.5%) had tumors with diameters greater than 5 cm (Table II).

Fifteen patients underwent simple excision of their tumor, 12 wide excision, 14 amputation above the joint proximal to the tumor, and ten amputation below the proximal joint; therefore 24/52 (46%) patients were treated with amputation.

Surgical treatment was used, either alone in 32 patients, or in combination with other modalities in 19 patients, and only one primary tumor was treated with radiation alone. Of the patients receiving combination treatments, six had surgery plus radiation, 10 surgery plus chemotherapy, and three had surgery plus radiation and chemotherapy.

The type of surgical treatment was related to the anatomic site. Thus of 14 patients with proximal lower extremity tumors, five were treated with amputation, whereas of 21 with distal lower extremity tumors, 15 were treated with amputation ($P < .01$). The anatomic location related also to the type of treatment rendered. Thus proximal lower extremity lesions were treated more frequently with combination of modalities, ie, surgery plus radiation or chemotherapy or both, which was used in nine of 14 patients, compared with its use in four of 21 patients with distal extremity tumors ($P < .05$).

The type of surgery for the primary tumor was related to the type of overall treatment in the sense that with amputations the use of combination of modalities was less frequent ($P < .001$). Thus of 24 patients with amputations, five patients received additional chemotherapy and one additional radiation; of 27 patients with simple or wide excision, five received additional radiation, five additional chemotherapy, and three additional chemotherapy and radiation.

TABLE I. Site of Tumor and Survival

Tumor Site	No. Patients	Median Survival (mo)	5-Year Survival (%)
Upper extremity, proximal	3	29.5	66.7
Upper extremity, distal	7	46.9	47.6
Upper trunk	4	36.0	50.0
Lower trunk	3	13.0	0.0
Lower extremity, proximal	14	18.5	12.8
Lower extremity, distal	21	67.5	58.7

TABLE II. Size of Tumor and Survival

Site	Tumor Diameter	No. Patients	Median Suvival, mo	5-Year Survival, %
All sites	<5 cm	13	91.7	72.7 ($P < .001$)
	>5 cm	31	28.2	33.1
Lower extremity, proximal	<5 cm	2	21.0	0.0
	>5 cm	11	14.2	20.2
Lower extremity, distal	<5 cm	10	101.3	77.8
	>5 cm	6	35.0	33.3

RESULTS

Local recurrence was noted in 18 patients. The relation of local recurrence to prior surgical treatment was of borderline significance; local recurrence was observed in three of 24 patients with prior am-

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From the Departments of Surgical Oncology (Drs Rajpal, Karakousis) and Biomathematics (Dr Moore), Department of Health of the State of New York, Roswell Park Memorial Institute, Buffalo.

Address correspondence to Dr Karakousis, Chief, Soft Tissue-Melanoma Service, Roswell Park Memorial Institute, 666 Elm St, Buffalo, NY 14263.

putation, four of 12 patients with wide excision, and 10 of 15 patients with simple excision. One local recurrence was actually persistence of the primary tumor after partial regression with radiation.

Local recurrences were apparently due to residual microscopic disease and in the case of amputations appeared because the plane of amputation was not carried at a sufficient distance from the tumor.

The role of adjuvant chemotherapy was difficult to evaluate because it was applied in a small number of patients and various protocols were used. There was a trend supporting the efficacy of adjuvant radiation in improving local control although the differences were not statistically significant. Thus of eight patients who had simple excision alone seven had local recurrence, whereas of five patients who had simple excision plus radiation two had local recurrence. Of five patients who had wide excision alone two had local recurrence, whereas none of three patients with wide excision plus radiation had local recurrence.

The five-year disease-free survival varied according to the surgical treatment: 6.6% for simple excision, 25% for wide excision, and 29% for the amputation group. However, the difference was not statistically significant, probably because of the small number of patients.

Local recurrence was managed with surgical treatment alone in eight patients, in combination with radiation or chemotherapy in three patients, and with radiation, chemotherapy, or both in seven patients. Of these patients, 11 (61.1%) remained free of further local recurrence. All 11 patients had been treated by surgery, either alone in eight patients or in combination with other modalities in three patients.

The overall five-year survival from initial diagnosis was 43.5% and median survival 41.5 months. The five-year disease-free survival was 21.2%. Survival varied significantly according to the anatomic site and the size of the primary tumor. Patients with tumors located in the distal extremity survived longer compared with those having tumors in the proximal extremity, the difference being significant in the lower extremity ($P < .01$, Table I). In 44 patients with accurately known diameter of tumor, patients having tumors smaller than 5 cm in diameter survived longer than those having tumors larger than 5 cm in diameter ($P < .001$, Table II). Each of these two variables, tumor size and location, produced consistent changes in survival, in the same direction as in the overall number of patients, when each was considered in isolation by maintaining stable the other (Table II). However, probably due to the small number of patients, tumor size remained statistically significant ($P < .05$) only among tumors located in the distal extremity.

TABLE III. Survival According to Treatment of Metastases

Treatment	No. Patients	Median Survival mo
Surgery alone	4	21.0
Surgery + chemotherapy	15	19.2
Surgery + radiation + chemotherapy	2	3.6
Chemotherapy alone	17	9.5
Radiation + chemotherapy	2	11.0

Survival varied also with the sex of the patient, but the difference was of borderline significance. Thus 35 male patients had a median survival of 39.9 months and a five-year survival of 36.7%, whereas the respective figures for 17 females were 61.0 months and 58.3%. For patients with tumors less than 5 cm in diameter the difference in survival by sex was significant. Thus six males had a median survival of 42 months and a five-year survival of 50%, whereas seven females had a median survival of 129.5 months and a five-year survival of 100% ($P < .05$).

Median and five-year survivals varied also with age but not significantly. Thus 12 patients younger than 20 years had a median survival of 58.1 months and a five-year survival of 63.6%, whereas for 40 patients 20 years or older the respective figures were 40.8 months and 39.1%. The differences in survival were smaller considering 35, 40, or 50 years as demarcation points.

Forty patients with metastases had a median survival from diagnosis of 35.5 months and a five-year survival of 29.5%, whereas 12 patients did not develop metastasis and all survived five years.

Organs involved by metastatic disease were the lungs in 38 (95%), bone in 11 (27.5%), distant soft tissue in 8 (20%), brain in seven (17.5%), and peritoneal seeding and regional lymph node metastasis in three patients (7.5%).

In the treatment of metastatic disease, 19 of the 40 patients with metastases were treated by surgical excision, usually in combination with chemotherapy. Two patients with incomplete resection of their metastases had in addition radiation and chemotherapy. Seventeen patients were treated with chemotherapy alone and two with chemotherapy plus radiation. Survival varied according to the treatment of metastases, but the difference was not statistically significant (Table III).

DISCUSSION

In the present series, swelling was the most common initial manifestation of synovial sarcoma. The most common location was the lower extremity as has been previously reported.[2] There was a 2:1 male preponderance as in another report.[3]

Metastasis to regional lymph nodes occurred in 7.5% of our patients. A low incidence of lymph node metastases was also reported by Ryan et al,[4] but in other reports the incidence is about 20%.[1,3]

The surgical treatment of the primary tumor in the extremities varied with the location; tumors located in the distal extremity were more frequently treated with amputation. This obviously reflects the need for wide margins, not easily obtainable in the distal extremity without amputation. When simple or wide excision was performed, more frequently a combination of modalities was applied. The high rate of amputations for tumors of the distal extremity reflects the policy in that period of time, whereas the need and indications for amputation at present for soft tissue sarcomas have been dramatically curtailed with the use of adjuvant radiation[5] or regional chemotherapy and radiation.[6] For synovial sarcomas, the current evidence indicates that adjuvant radiation after local resection reduces the incidence of local recurrence.[4]

In the present study adjuvant radiation appeared to reduce the rate of local recurrence, but the difference was not statistically significant, probably because of the small number of patients. However, in our experience as of 1977[5] and the experience of Rosenberg et al,[7] adjuvant radiation appears to reduce the incidence of local recurrence. Thus in patients with primary soft tissue sarcomas treated at RPMI between July 1977 and December 1980 (minimum follow-up 30 months) the incidence of local recurrence following surgical excision and radiation was 5.3% (2/38 patients), whereas that following wide excision alone was 35% (12/34 patients, $P < .005$). In this series, adjuvant radiation was given only to patients with surgical margin 2 cm or less at any site around the tumor. Six patients with synovial sarcoma were seen in this period. One of them with synovial sarcoma of the elbow was treated with amputation and chemotherapy, but later had systemic recurrence and died. Five patients were treated with excision and adjuvant radiation. One of the five with recurrent synovial sarcoma of the chest wall had local recurrence outside the field of radiation, whereas the other four with extremity synovial sarcomas remain free of disease.

The local recurrence rate of 34.6% in the present series falls within the range observed in soft tissue sarcomas,[8] but higher local recurrence rates have been reported for synovial sarcomas.[9] Local recurrence observed more frequently following simple excision of the tumor. Surgical treatment (alone or with other modalities) achieved local control of the recurrent tumors in 11 patients, whereas treatment with radiation or chemotherapy or both controlled none of the recurrent tumors in seven patients.

Survival was significantly longer ($P < .001$) in patients with tumor less than 5 cm in diameter (median 91.6 months) compared to that of patients with tumor larger than 5 cm in diameter (28.2 months), as has been previously indicated.[2] Survival was also longer among patients with tumors in the distal lower extremity compared to those with tumors in the proximal lower extremity ($P < .05$). Of these two variables, tumor size and anatomic location, tumor size was the dominant one since it continued to remain significant when the other variable was maintained stable by considering only one anatomic location.

Female patients and those younger than 20 years had higher survival, as previously reported,[2,3] but the difference was not significant in our series. However, the difference according to sex approached borderline significance and became significant in favor of the females among patients with tumors less than 5 cm in diameter.

Case Report

The patient shown in the figure manifested symptoms suggestive of carpal tunnel syndrome in July 1977. Her left wrist was explored and a suspicious piece of tissue removed which on histologic examination proved to be synovial sarcoma. She was seen in August 1977 at RPMI, had no clinical evidence of tumor, and was eager for restorative surgery. An elliptical incision was made around the previous incision, flaps were raised, the palmaris longus divided proximally, and then in continuity the flexor retinaculum and palmar aponeurosis were removed. Biopsy samples from the surgical bed were negative, but in the removed specimen there were microscopic tumor extending to the line of resection. After operation she received 6,000 rads of radiation. Six years later she remains free of disease.

Appearance of hand and wrist six months after excision of synovial sarcoma of the wrist and four months following adjuvant radiation.

Forty patients manifested metastatic recurrence involving primarily the lungs. Nineteen patients who had resection of the metastatic lesions, usually with chemotherapy, subsequently survived a median of 19.5 months, whereas 17 patients who had chemotherapy alone had a median survival of 9.5 months. However, the improved median survival of patients with surgical excision of their metastases is probably the result, at least in part, of lesser amounts of tumor which were amenable to resection. Surgical resection of pulmonary metastases from soft tissue sarcomas is a well-established practice due to the peculiarity of these tumors to involve predominantly, and initially almost exclusively, the lungs. This practice is more successful in patients with long disease-free intervals prior to recurrence, indicating a long tumor-doubling time.[10,11] In selected cases, a five-year survival of 35% has been achieved with resection of pulmonary metastases from synovial sarcoma, usually without chemotherapy.[12]

It was difficult to evaluate the effect of chemotherapy in this series because of the multiplicity of protocols used in that period and therefore the small number of patients in each protocol. However, a response rate of up to 50% has been reported in the treatment of metastatic synovial sarcoma with chemotherapy.[4]

The overall median survival from diagnosis in our patients was 41.5 months, the five-year survival 43.5% and the five-year disease-free survival 21.5%. Among patients with metastatic recurrence the median survival after diagnosis of metastatic disease was 14 months and the five-year survival 2.5%.

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A painless mass in the left thigh of an 11-year-old girl

CASE HISTORY

Lawrence Weil, MD (Resident in Radiology): An 11-year-old girl was brought to this institution, complaining of a proximal left thigh mass of approximately three months' duration. She remembered sustaining mild blunt trauma to the area three months prior to admission during gymnastics class at school. The mass was noted to be essentially painless and there had not been any noticeable change in size over the past three months. She denied weight loss, fever, or any other constitutional symptoms.

Physical examination revealed a nonpulsatile proximal anterior left thigh mass measuring approximately 10 cm in width and extending 15 cm distally to the mid thigh. The circumference of the left thigh exceeded the right by 5 cm. The overlying skin was slightly warm to touch, although no palpable tenderness could be elicited. No neurologic deficits were present, and there was full range of motion of both hips, knees, and ankles.

Laboratory examination included a normal hemoglobin and hematocrit of 13.3 g/dL and 38%, respectively, and a WBC count of 7,800/mm^3. Other data were within normal limits with the exception of an elevated alkaline phosphatase of 148 IU (normal, 13 to 20). Plain radiographs, computed tomography (CT), bone scan, and angiography were obtained.

RADIOLOGIC DISCUSSION

E. Mark Levinsohn, MD (Associate Professor, Department of Radiology): The first radiographs shown (Fig 1) are anteroposterior and frog-leg lateral views of the proximal left thigh. There is a 5 × 7-cm soft tissue mass adjacent to the anterior surface of the femur. Within this mass are small scattered amorphous calcifications. A flat plane separates the anterior surface of this mass from the muscles of the proximal thigh. The underlying bone is normal.

The next examination is an unenhanced CT scan at the level of the upper thighs (Fig 2). A large soft tissue mass is demonstrated which is bordered by the femur and iliopsoas muscles posteriorly; the sartorius, rectus femoris, and tensor fasciae latae muscles anteriorly and laterally; and the femoral vessels and pectineus muscles medially. Again noted are amorphous calcifications which are scattered throughout the lesion. A contrast enhanced CT scan of the thigh (Fig 3) was next performed. Puddled areas of increased attenuation are scattered throughout the lesion. These indicate areas of hypervascularity. An arteriogram (Fig 4) shows medial displacement of the superficial femoral artery. Extensive neovascularity originating in large

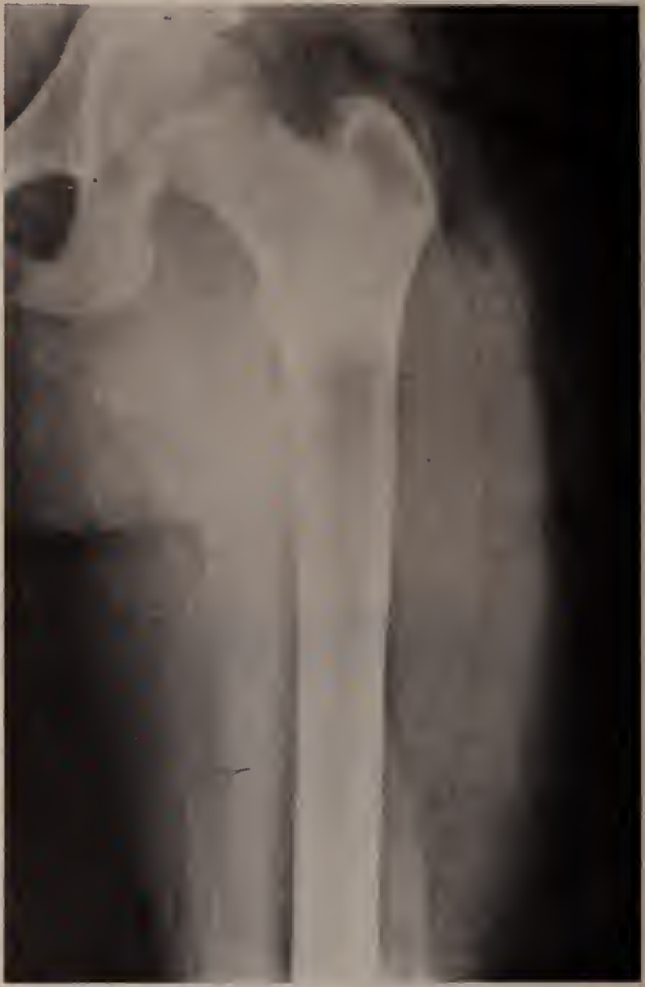
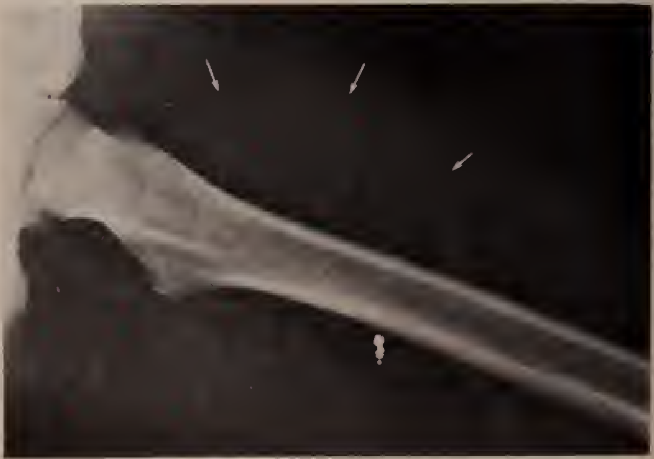


FIGURE 1. Anteroposterior (above) and frog-leg lateral (below) radiographs of the proximal left thigh show a large soft tissue mass anteriorly containing tiny calcifications. Underlying bone is normal. Arrows indicate anterior extent of soft tissue mass.



Edited by Michael E. Berlow, MD, Assistant Professor, Department of Radiology and Bedros Markarian, MD, Associate Professor, Department of Pathology, State University of New York, Upstate Medical Center, Syracuse, NY 13210.

part from the profunda femoral artery is present throughout the lesion.

The differential diagnosis of this lesion includes primary bone malignancy, myositis ossificans, hemangioma, synovial sarcoma, and rhabdomyosarcoma. Primary bone sarcoma is unlikely because of the lack of involvement of the bony cortex and bone marrow as seen on the CT scan. Extraskeletal osteogenic sarcoma could, however, present with an appearance such as this. Myositis ossificans shows many of the features seen in this case. The patient's age, the presence of a calcified soft tissue mass in the anterior thigh, and the hypervascularity are all seen in patients with myositis ossificans. The punctate calcifications scattered throughout this lesion would be unusual in myositis, which more commonly shows a well developed peripheral calcification leading to heterotopic bone formation. Similarly, the punctate amorphous calcifications are not typical for hemangioma. Rhabdomyosarcoma is an infrequent but not rare tumor which is found in the extremities in this age group. When present it may calcify and is frequently hypervascular. There are somewhat more calcifications seen here than are usual for rhabdomyosarcoma. Synovial sarcoma is an uncommon malignant neoplasm which is most frequently found in the third and fourth decades. A hypervascular soft tissue mass may be present and calcification is found in 20% to 30% of cases.

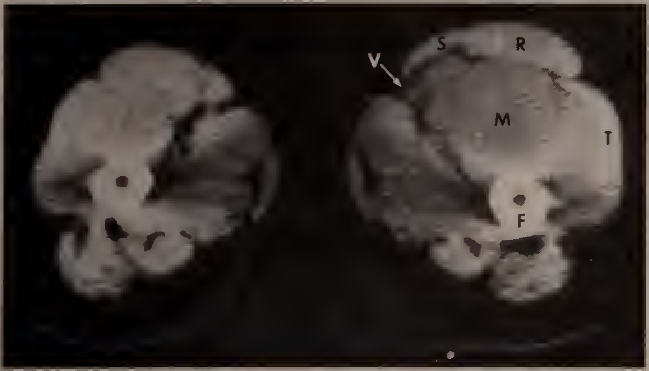


FIGURE 2. Unenhanced CT scan at level of upper femur shows scattered amorphous calcifications in center of soft tissue mass. Bony cortex and marrow space are normal. T—tensor fascia latae muscle, R—rectus femoris muscle, S—sartorius muscle, F—femur, V—femoral vessels.

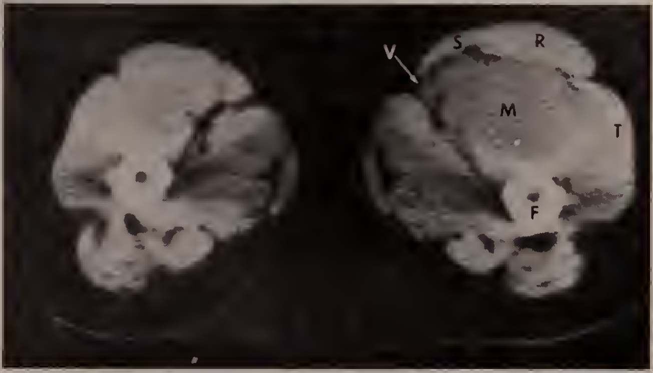


FIGURE 3. Enhanced CT scan at level of proximal femur shows contrast pooling within this vascular lesion.

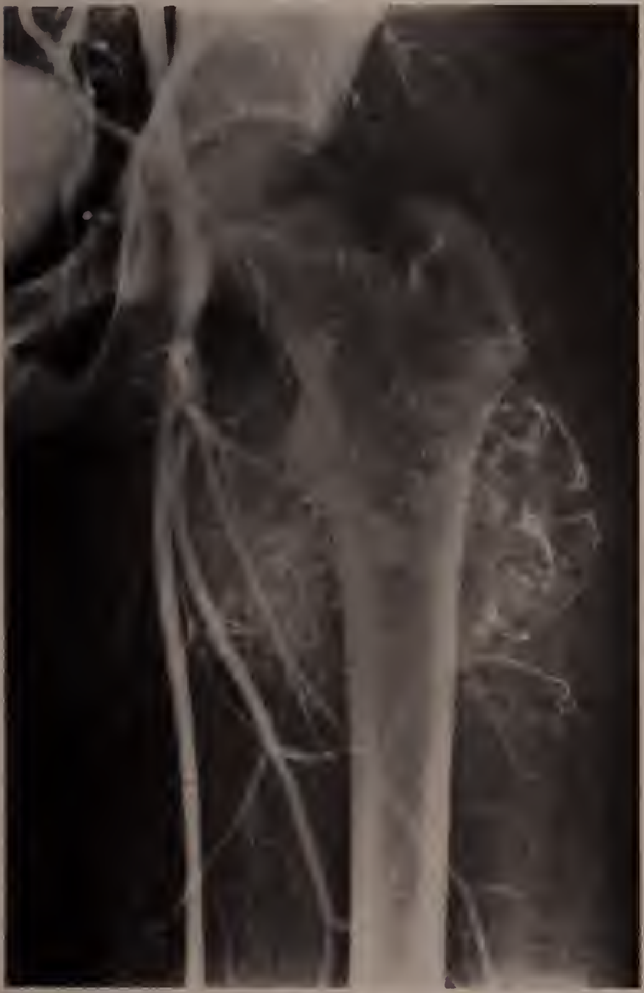


FIGURE 4. Film from arteriogram shows medial displacement of superior femoral artery and extensive neovascularity originating from profunda femoris artery.

Dr Levinsohn's Diagnosis

Soft tissue sarcoma, most likely synovial sarcoma.

PATHOLOGIC DISCUSSION

Dr Weil: An open biopsy of the soft tissue mass was performed.

Bedros Markarian, MD (Associate Professor, Department of Pathology): The tissue submitted was a biopsy of the left thigh mass, measuring 2.5 cm in greatest dimension. The tissue had a pale pink color and was firm in consistency. Microscopically, the tumor presented a primitive spindle cell appearance, which had a prominent vascular pattern in some areas (Fig 5). This vascular pattern is similar to that described in hemangiopericytoma. However, the reticulum stain did not confirm the typical perivascular pattern described for hemangiopericytoma.[1] Stains for mucin, which is present in biphasic synovial sarcomas, and the myoglobin immunoperoxidase stain are negative. Biphasic synovial sarcomas have a malignant spindle cell, fibrosarcomatous pattern combined with clefts and spaces lined by epithelial-like cells giving it a pseudoglandular appearance. This is a manifestation of synovial mesothelial cells which are the cell of origin of this neoplasm. Many of the pseudoepithelial islands are associated with the presence of mucin-like

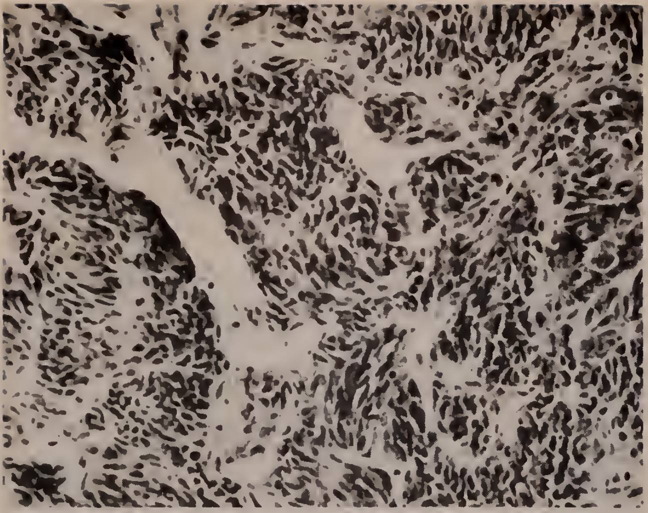


FIGURE 5. Photomicrograph shows islands of pleomorphic spindle tumor cells separated by rich network of vascular spaces. (Original magnification × 425.)

substance. There is also a monophasic variant of a synovial sarcoma in which the epithelial-like pattern may be quite rare and, consequently, is not histologically identified in the examination of the neoplasm. Electron microscopy shows primitive mesenchymal cells with scant glycogen. Our conclusion on this case was that this tumor represents a monophasic synovial sarcoma. The patient later had radical surgery at Memorial-Sloan Kettering but I have not had an opportunity to review any of their material. Their diagnosis was also synovial sarcoma.

DISCUSSION

Dr Weil: Synovial sarcoma is an uncommon soft tissue tumor. These tumors usually arise from the synovium of the joint capsules, bursae, or tendon sheaths. The point of origin of the tumor in most cases cannot be identified, and a direct connection with synovium is usually not demonstrable. There is a high rate of local recurrence among patients with this neoplasm, and death due to the disease occurs in a large percentage of cases. Synovial sarcoma occurs in the extremities in 94% of cases, most commonly in the leg. Rare locations include the abdominal and thoracic walls, pelvis, and buttocks. The greatest incidence is during the third, fourth, and fifth decades. The most common presentation is a mass or swelling, which may or may not be painful. There is a slightly better prognosis for tumors involving the lower extremities than for those in the upper extremities.[2]

The typical roentgen appearance is a soft tissue mass arising near a joint. Calcifications appear within the lesion in approximately 30% of cases. Secondary bone involvement is seen in about 10% of patients. Additional radiographic findings include joint effusion, osteoporosis, narrowing of the joint space, and periosteal new bone formation. Distant metastases to the lung and less commonly to the skeleton occur. Bone metastases are primarily lytic but osteoblastic vertebral lesions may be seen.

This case demonstrates a multimodality approach to imaging musculoskeletal masses. In particular, it emphasizes the role of computed tomography in the evaluation of these tumors. The precise anatomic delineation of primary soft tissue tumors by CT, as well as the soft tissue masses associated with primary bone sarcomas, is superior to other imaging modalities. The relationship of soft tissue tumors to adjacent bones, blood vessels, or large nerves can be determined with CT. Primary skeletal neoplasms such as osteosarcoma and Ewing's sarcoma can spread through the medullary cavity. CT can show image changes in the normally low density fatty marrow indicating areas involved with tumor.[3] This information significantly affects patient management. In the past, many primary malignant tumors of the extremities in young patients were managed by amputation. With the development of intensive chemotherapy, limb conservation by means of en bloc or muscle group resection is practiced wherever possible.[4] CT is of considerable benefit in determining whether such a procedure is feasible.[5] In addition, it accurately establishes radiation portals.

Although CT offers excellent anatomic resolution, it should not be used indiscriminately. Conventional radiographs and tomograms should remain the primary imaging procedures in the diagnosis and evaluation of extremity masses.[6] With the exception of difficult anatomic areas, notably the sacrum and vertebral appendages, demonstration and characterization of areas of bone destruction are better performed by conventional methods.[7] In addition, it must be remembered that generally the density of a mass is nonspecific and the precise histologic character cannot be determined on the basis of CT. The only exception to this is the characteristic fat-containing lipoma.[8]

Angiography has also been used to evaluate the extent of soft tissue masses. Although CT is more accurate than angiography, important indications for angiography remain. These include the demonstration of a small tumor in a distal part of an extremity which may not be visualized on CT, the evaluation of the vascular supply of a mass, and the arterial runoff to the distal portion of an extremity where a more proximal mass exists. Furthermore, percutaneous arterial embolization of hypervascular lesions may be a consideration, usually as an adjunct to surgery.

It should be remembered that the various imaging modalities are complimentary. Although more sophisticated techniques are now available, detection and differential diagnosis of musculoskeletal masses are often based on plain radiographs. CT is most useful in determining the extent of disease, which substantially influences the planning of therapy.[9] On the horizon, nuclear magnetic resonance is another modality that offers great potential for evaluation of these lesions.

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Back pain and rapid neurologic deterioration in an elderly woman

CASE PRESENTATION

Karl Goodman, MD (Resident, Department of Medicine): A 68-year-old woman was admitted with progressively increasing back pain for two months. Compression deformities and osteoarthritis of the lower spine were visible on x-ray; the pain had worsened during the two weeks prior to admission, and she was treated with zomepirac sodium (Zomax) and piroxicam (Feldene).

During the three months prior to admission, the patient had had occasional palpitations, two-pillow orthopnea, and swelling of both lower extremities, a condition diagnosed by her physician as congestive heart failure. A chest x-ray at the onset of symptoms was reported to be normal.

Examination of the patient in the emergency department revealed bilateral basal pulmonary rales and bilateral leg edema; following injection of a diuretic, the patient was admitted to the hospital.

The past medical history and systems review were otherwise negative, except that the patient had taken 12 or more ounces of vodka per day, up to one month prior to admission.

Physical examination on admission revealed the patient to be in moderate distress and with a mild tremor. The blood pressure was 110/70 mm Hg, the pulse 100, and the respiratory rate 20 per minute; the temperature was 37.2°C (99°F). Bibasilar pulmonary rales were noted on inspiration, without wheezing or rhonchi; the cardiac rhythm was regular with a grade 2/6 systolic ejection murmur loudest at the tricuspid area. Two-plus pitting edema of both ankles was present. There was restriction of straight-leg raising on the left, with accentuation of back and extremity pain. The skin showed no lesions. The patient was tremulous and unable to stand due to back pain; neurologic examination was limited but showed no gross deficits.

The initial urinalysis was negative, except for two to four white blood cells and 12 to 20 red blood cells per high power field. The hemoglobin was 10.2 g/dL, hematocrit 29.9%, and white blood cell count 11,900/mm^3 with 83% mature polymorphonuclear leukocytes. The platelets appeared adequate in number on smear. The prothrombin time and partial thromboplastin time were normal. The serum albumin was 2.4 g/dL (normal, 3.5 to 5.0 g/dL); the serum calcium, phosphorus, and cholesterol levels were normal. The lactic dehydrogenase was 270 U/mL (normal, 60 to 120 U/mL), SGOT 45 U/mL (normal, 10 to 40 U/mL). The blood urea nitrogen (BUN) was 14 mg/dL, the creatinine 0.9 mg/dL, and the blood glucose 121 mg/dL; the serum potassium 3.5 mEq/L, and other serum electrolyte levels were normal. Repeat urinalysis was entirely normal. The arterial blood gas analysis revealed a pH of 7.41, pCO$_2$ 29 mm Hg, pO$_2$ 68 mm Hg, bicarbonate 18 mEq, base excess 4 mEq, and oxygen saturation 94%.

During the five-day hospital course, the temperature was normal except for elevations on the second hospital day to 37.3°C and 38.3°C (99.2° and 101°F), and a rise on the fifth hospital day to 37.3°C. On the second hospital day, the patient showed evidence of lethargy, confusion, aphasia, and generalized weakness more marked in both lower extremities. There was an equivocal plantar response on the right and an extensor plantar response on the left. The neurologic consultant's impressions were those of diffuse cerebral dysfunction, with cerebellar involvement, possibly related to alcohol, together with chronic alcoholic myopathy. A spinal cord lesion was also suspected. Lumbar puncture revealed normal spinal fluid, with normal chemical findings and cell counts, and negative cultures and smears for bacteria on Gram's and acid-fast stains. The orthopedic consultant noted tenderness on percussion over the thoracic and lumbar vertebrae, as well as the x-ray evidence of osteoporosis, with compression fractures of T-6,8,10,12, and of L-2. A bone scan was suggested.

The cardiology consultant thought the history compatible with rapidly progressive congestive heart failure. His examination indicated diminished breath sounds bilaterally, rales over the lower one third of the right chest posteriorly, cardiac enlargement with a systolic heave, and a loud, harsh systolic murmur, grade 2–3/6, at the left lower sternal margin radiating to the apex and around to the back. He interpreted the chest x-ray as indicating cardiac enlargement and congestive failure. The echocardiogram showed possible enlargement of the left auricle, a small pericardial effusion and evidence of vegetations on the mitral valve.

Six blood cultures were drawn; the patient was treated promptly with penicillin, oxacillin sodium, and gentamicin sulfate. Repeat urinalysis was normal. An electromyogram and a computerized tomographic scan of the brain were ordered. Thiamine and potassium chloride were administered together with three doses of zomepirac sodium

On the following (third) hospital day, the patient's aphasia was improved but she continued to be disoriented as to time and place. She refused to eat, was incontinent of urine and persistently tremulous. Her blood pressure remained in the range of 90/50, and a few rales were noted

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Based on the clinicopathologic conference (CPC) held at the New York Infirmary-Beekman Downtown Hospital on April 19, 1983.

Moderator: Irwin Sharkey, MD, Chief of Medicine; *Clinical Discussion:* Perry Berg, MD, Attending Physician; *Pathology Presentation:* Solange Abunassar, MD, Attending Pathologist.

Editor, JOHN T. FLYNN, MD.

Address correspondence to Dr Flynn, Consulting Editor, *New York State Journal of Medicine*, PO Box 5404, 420 Lakeville Rd, Lake Success, NY 11042.

at the lung bases. The neurologic consultant suspected in addition a neuromyopathy and a possible alcoholic myelopathy. On this day, the patient was given digoxin 1.0 mg in divided doses.

Early on the morning of the fifth hospital day, the patient became diaphoretic and unresponsive; her blood pressure was 150/80 initially and later fell to 110/70. Her pulse was 106 and respiratory rate 28 per minute; her temperature was 37.3°C (99.2°F) on one observation. The left pupil was smaller than the right; the deep tendon reflexes were only midly active with bilateral Babinski responses. The blood chemical findings were unchanged. The EKG showed two to three ventricular premature contractions per minute. Gentamicin and oxacillin were discontinued, penicillin was increased to 3 million units every four hours; the patient was intubated and given assisted respiration. Steroid therapy was begun, together with mannitol, dopamine drip, plasmanate, Ringer's lactate, and norepinephrine bitartrate (Levophed) injection.

The neurologist found the patient's pupils to be equal but fixed to light with no corneal reflexes; there was a flaccid paralysis of all extremities, with bilateral Babinski responses. His impression was of diffuse cerebral dysfunction, and cerebral angiography was considered. Following transfer to the intensive care unit, the Swan-Ganz catheter indicated a right auricular pressure of zero, a right ventricular pressure of 21/0, and a pulmonary artery pressure of 21/0. Shortly after transfer, the blood pressure fell progressively to 40/20, the pulse rose to 140 and later fell to 75 per minute, with numerous auricular premature contractions. Despite continued efforts at maintenance of vital functions, the patient's cardiac activity ceased and she was pronounced dead on the afternoon of the fifth hospital day.

Clinical Discussion

Perry Berg, MD (Attending Physician): A 68-year-old woman was admitted with increasing back pain and evidence of congestive heart failure followed by rapid deterioration in her neurologic status and death on the fifth hospital day. Her alleged abuse of alcohol seems unrelated to this sequence of clinical events.

Earlier x-ray films of the spine showed vertebral body compressions, typical of osteoporosis, readily accounting for her back pain and the difficulty with straight-leg raising. Osteoarthritic changes in the facet-joints of the vertebral column may be associated with spinal stenosis and sometimes exceedingly severe back pain; nevertheless this woman's complaints rather suggest vertebral compression and possibly intervertebral disk disease. However, her progressive back pain with radicular radiation and recurrent fever could be indicators of a paraspinal epidural abscess. Early in such a process, ordinary roentgenograms are of little help. The diagnosis requires a high index of suspicion, based on the patient's symptoms and findings, especially a sharply localized area of tenderness. However, the orthopedist's finding of acute but diffuse tenderness over the thoracic and lumbar spine, and the x-ray changes are more compatible with osteoporosis. We should not dismiss entirely, however, the possibility of epidural abscess.

At the time of admission, the initial cardiac findings suggest tricuspid insufficiency, but without confirmatory physical signs, such as jugular venous distention, hepatic enlargement, or visible venous pulses in the neck. There were no signs of right-sided heart failure, except perhaps the peripheral edema. The cardiologist subsequently noted a loud harsh systolic murmur at the apex, radiating around to the back, compatible with mitral insufficiency, and also with papillary muscle dysfunction, most likely on the basis of infection.

May we review the x-rays now?

Virgiliu Nekula, MD (Attending Radiologist): Three months before admission, the patient's chest x-ray showed only borderline cardiomegaly. There were some osteoarthritic changes of the dorsal spine.

The chest x-ray on the day of admission showed pulmonary congestion and blunting of the left costophrenic angle, most probably due to fluid—findings compatible with congestive heart failure. The chest film on the following hospital day showed an increase in the pulmonary congestion.

X-ray films of the spine on admission showed compression of vertebral bodies T-8,10, and 12; there are anterior osteophytes on the margins of these vertebral bodies. These findings suggest osteoarthritis and osteoporosis of the dorsal spine; the paraspinal lines look to be within normal limits.

In the lumbar spine, there is partial collapse of L-1, collapse of L-2, and a narrowing of the intervertebral space L-5:S-1. These findings again suggest senile osteoporosis, together with osteoarthritis. The cervical spine also shows osteoarthritic changes in the posterior joints, together with narrowing of the intervertebral space C-5:C-6, suggesting intervertebral disk disease.

On the fifth hospital day, the chest x-ray showed the Swan-Ganz catheter tip in the right pulmonary artery, and also showed that the radiologic evidence of heart failure had not changed.

Dr Berg: Multiple myeloma sometimes appears on x-ray as diffuse osteoporotic changes of the spine, indistinguishable from primary osteoporosis. We have no information here about the levels of serum globulin, immunoelectrophoretic patterns, or bone marrow studies which might rule out multiple myeloma. Congestive heart failure related to myeloma would imply cardiac amyloidosis, which however presents as a restrictive cardiomyopathy, commonly accompanied by signs of right-sided failure, which are not present here. With a cardiomyopathy, echocardiography usually demonstrates very dilated cardiac chambers or thickened walls, or an asymmetrically hypertrophied chamber without anterior systolic motion of the mitral valve; none of these are reported in our patient. Only an enlarged left atrium, a small pericardial effusion, and suspected vegetations on the mitral valve are mentioned. Also, myeloma could hardly explain the other clinical findings, especially the rapidly progressive cerebral dysfunction.

I prefer to believe that the clinical facts and laboratory findings best support a diagnosis of infective endocarditis. Echocardiographic evidence of mitral vegetations frequently relates to a rapidly progressive clinical course. In this patient, I believe that the echocardiographer's impression, even though tentatively offered, is a clue of great weight.

Other laboratory tests offer only limited help. The microscopic hematuria and bacteriuria are insufficient to suggest a renal origin of the back pain. Despite the low serum albumin, there is no other significant laboratory evidence of advanced hepatic cirrhosis. The low serum potassium level is compatible with prolonged diuretic therapy.

Her neurologic status was and is difficult to define. The generalized weakness in both lower extremities, an equivocal right plantar response, and a positive Babinski response on the left suggest right-sided upper motor neuron disease. Cerebellar and diffuse cerebral dysfunction were súspected, possibly related to alcohol, but no elements of a Wernicke's syndrome were evident. During her hospital course, the patient developed intermittent aphasia, which suggests a more definite cerebral localization, provided we know whether the patient was right- or left-handed. A left-handed patient with aphasia and a left Babinski response would be affected by right cerebral dysfunction. The patient's tremor, inability to walk due to back pain, stupor, and subsequent coma made cerebral localization even more difficult.

Throughout her hospital stay, the patient had two or three temperature elevations; she had an an ill-defined but serious cardiac lesion, severe back pain with a radicular distribution and progressive cerebral findings ending in death. All these can be due to infective endocarditis. I assume that the six blood cultures drawn before antibiotic therapy were positive. Suspect organisms would include staphylococcus, *Streptococcus fecalis*, and enterococcus. The antibiotic therapy no doubt accounted for her minimal fever but otherwise influenced her hospital course very little. The small number of red and white blood cells in her urine with an elevated BUN suggests renal glomerular involvement, either by a glomerulonephritis or by embolism or by both.

Endocarditis in patients in their 60s and 70s involves bicuspid aortic valves more often than valves damaged by rheumatic fever. However at no point was the murmur in this case clearly established as being related to aortic stenosis. I believe that the infected vegetations involved the mitral valve. Cerebral embolism may have been followed by propagation of thrombi, intracranial bleeding, and the sequence of central nervous system symptoms as were reported.

So-called nonbacterial thrombotic endocarditis in the presence of prolonged chronic disease involves the formation of sterile thrombi especially on the mitral valve. This process may evolve into infective endocarditis, but by itself may give rise to cerebral emboli, with resulting localizing neurologic findings or psychosis. However, I believe that the valvular vegetations here were infected.

The observations via the Swan-Ganz catheter, if accurate, suggest that the initial congestive failure had responded to treatment; and that death was due to progressive cerebral dysfunction.

In summary, I believe that this patient developed infected vegetations on a cardiac valve, most probably the mitral, which may or may not have been previously deformed. She then sustained widespread embolism and infarctions in all the major organs, including cerebral infarction, hemorrhage, and possibly infection. Brain-stem herniation may have occurred, probably due to increasing cerebral edema. The presenting symptom of back pain was most probably due to a coincidental senile osteoporosis with vertebral compression, but let us keep spinal epidural abscess in mind also.

CLINICAL DIAGNOSES

Infective endocarditis, most probably involving the mitral valve.

Widespread embolism and infarction secondary to the first diagnosis.

Embolic infarction of the brain, probably with cerebral abscess formation and hemorrhage.

Senile osteoporosis with secondary collapse of vertebral bodies and nerve-root compression.

Possible epidural abscess secondary to the first diagnosis.

PATHOLOGY PRESENTATION

Solange Abunassar, MD (Attending Pathologist): The diagnosis at autopsy was bacterial endocarditis. The organism cultured from the blood during life was alpha hemolytic *Streptococcus*, *viridans* group. Postmortem cultures were not taken, since the autopsy was performed seven days after death.

The heart weighed 350 g, at the upper limits of normal for a female. Anatomically, the valves were normal; however, each mitral leaflet presented a friable gray-yellow vegetation, approximately 3 cm in diameter. A 0.5-cm perforation extended through the posterior valve leaflet, roughly in the center of its vegetation (Fig 1). The left atrium showed granular areas of focal acute endocarditis. The myocardium was flabby and pale.

Under the microscope, the vegetations were seen to consist of amorphous masses of fibrin, platelets, cellular debris, acute inflammatory cells, and gram-positive cocci, with sufficient organization to indicate their presence for some time. Platelet thrombi in the intramyocardial coronary artery branches and the many microscopic myocardial abscesses no doubt resulted from showers of emboli from the vegetations (Fig 2). There was no evidence of myocarditis, and the patchy myocardial fibrosis present was not truly characteristic of alcoholic cardiomyopathy.[1]

The liver weighed 1,450 g; the capsular and cut surfaces were tan in color and slightly flabby. The inflammatory cellular infiltrate seen under the microscope in portal areas and in sinusoids no doubt were the result of sepsis. There was no evidence of alcoholic hepatitis nor cirrhosis. Changes in the liver in alcoholic patients with congestive heart failure can proceed from congestion with centrilobular necrosis, to central vein sclerosis ("cardiac sclerosis"), and finally to fibrosis of varying degree, ie, cardiac cirrhosis.[1] In this patient, cardiac sclerosis was present. (In a recent clinical study, alcoholic cardiomyopathy and alcoholic hepatitis or cirrhosis appeared to be mutually exclusive.[1])

The cranial cavity contained a recent subdural hematoma in the right temporal region; recent subarachnoid hemorrhage extended from the right temporal to the right occipital lobe. Several areas, including the hippocampus, midbrain, and pons showed microscopic foci of early abscess formation. A few small vessels contained platelet thrombi but no gross emboli (Fig 3). No changes in the brain related to alcohol could be identified; postmortem autolysis was evi-

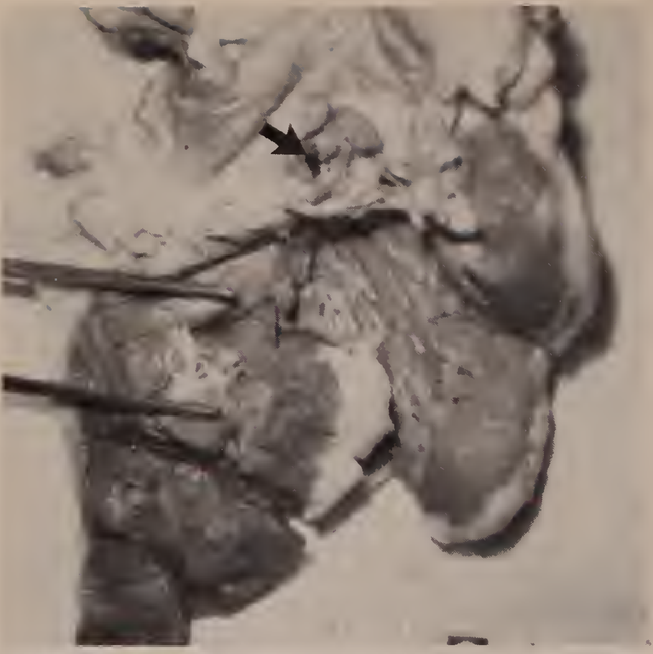

FIGURE 1. Interior of left ventricle showing perforation (arrow) of posterior mitral leaflet in center of bacterial vegetation.

dent. The spinal cord and peripheral nerves were grossly unremarkable.

The kidneys in this patient were of normal weight. The upper pole of the right kidney contained a 0.4-cm recent infarct. Under the microscope, recent infarcts and microabscesses probably secondary to microemboli, were evident; however, some such lesions may have been initiated by a focal necrotizing vasculitis present in small arteries in the kidneys. A similar vasculitis was also present in the perirenal fat.[2] Other renal lesions included focal and segmental endocapillary and extracapillary glomerulonephritis, probably representing an immune-complex nephritis initiated by circulating antigen-antibody complexes (Fig 4). These renal lesions no doubt contributed to the hematuria and the findings on urinalysis; however, unlike the diffuse type of immune-complex glomerulonephritis in infective endocarditis, these focal lesions rarely lead to renal failure.[3]

The spleen weighed 250 g and contained several old and recent infarcts, commonly found in patients with infective endocarditis.

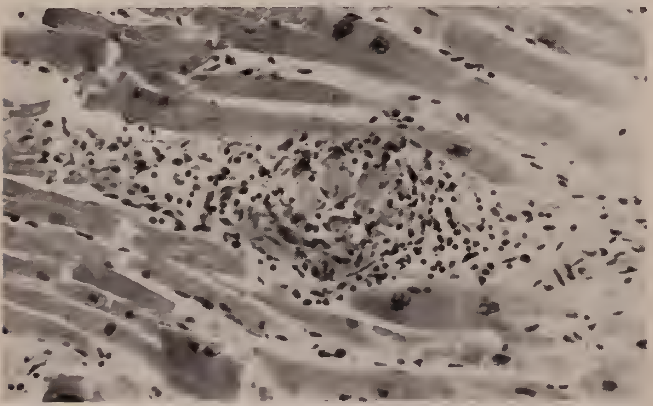

FIGURE 2. Myocardial abscess formation secondary to septic coronary artery embolism. (Hematoxylin and eosin, original magnification ×42.)

The upper lobe of the left lung contained a recent 5-cm infarct, secondary to a pulmonary artery thromboembolism probably originating in leg of pelvic veins. A hematoma weighing about 300 g and covering the lateral aspect of the left lung may have been secondary to a ruptured mycotic aneurysm. Focal vasculitis, with aneurysmal dilatation and microabscess formation, was found in the thyroid (Fig 5). The pancreas showed microabscesses but no alcoholic changes. The esophageal mucosa presented superficial erosions, possibly related to intubation.

Several sequelae of infective endocarditis in this patient are worthy of note, especially the central nervous system and musculoskeletal complications. Neurologic complications in endocarditis were emphasized by Osler a century ago[4] in referring to the classic triad of fever, heart murmur, and hemiplegia. Despite other changes in the presentations of bacterial endocarditis since the advent of antibiotics, the tendency to develop neurologic complications has persisted; studies at the Mayo Clinic and at the Massachusetts General Hospital report incidences of 29% and 39%, respectively.[2,5] Neurologic complications can precipitate early symptoms and even constitute the chief complaint.[2] The presence of neurologic complications enhances the mortality of infective endocarditis by a factor of three.[5] Central nervous system emboli occur more commonly in endocarditis due to *Streptococcus viridans* and tend to originate from mitral valve vegetations.[5]

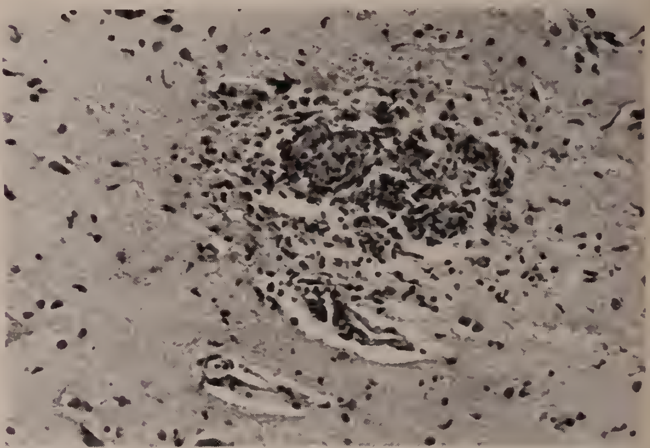

FIGURE 3. Microabscess formation in cerebral tissue. (Hematoxylin and eosin, original magnification ×25.)

The clinical syndromes resulting from microscopic emboli are more diverse than those of gross embolism, with altered levels of consciousness, seizures, and fluctuating neurologic signs.[5] Of course, some neurologic symptoms such as headache, dizziness, vertigo, irritability, lethargy, insomnia, and drowsiness may be due to fever or to bacterial toxins in endocarditis rather than due to emboli, and they may be further intensified by anemia and congestive heart failure in some patients.[6] This patient's microscopic cerebral emboli and microabscesses partly explain the neurologic findings. However, in the absence of trauma, spontaneous rupture of a mycotic aneurysm appears to be the most likely cause of the subarachnoid and subdural hemorrhages and can account for the rapid deterioration of the patient.[5]

Mycotic aneurysms in bacterial endocarditis most likely

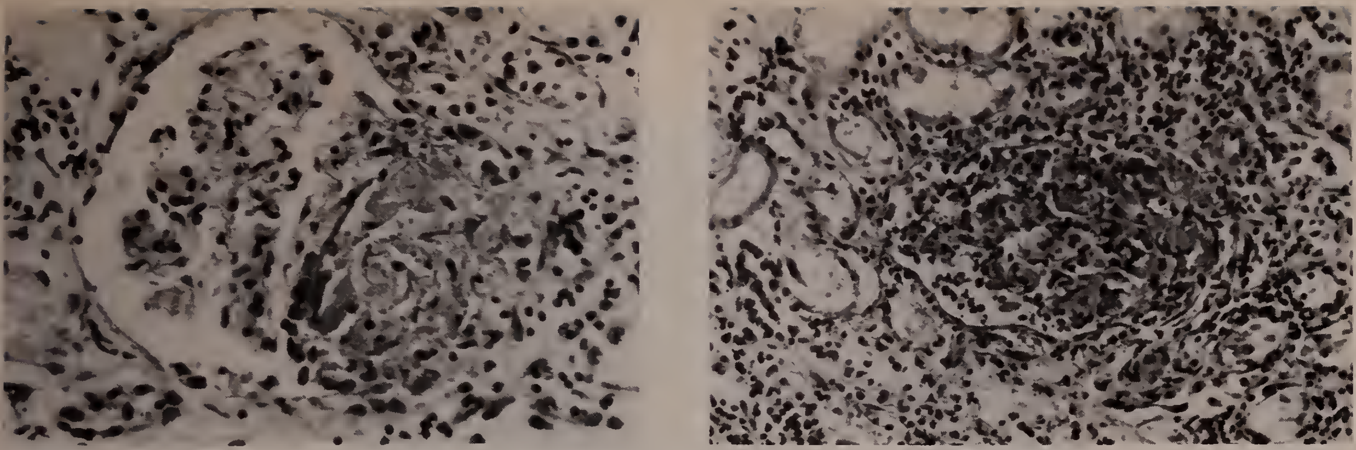

FIGURE 4. Glomerulonephritis secondary to bacterial endocarditis (hematoxylin and eosin). Left, endocapillary (original magnification ×25). Right, extracapillary (original magnification ×42).

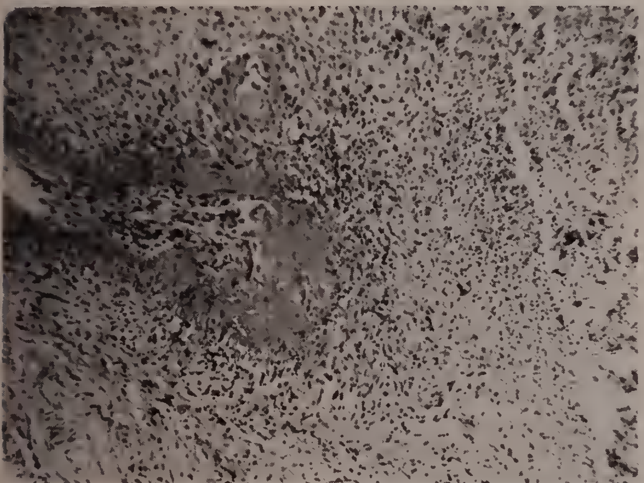

FIGURE 5. Focal acute necrotizing vasculitis with microabscess formation, in thyroid gland. (Hematoxylin and eosin, original magnification ×10.)

originate from an embolus to the artery, with subsequent progressive inflammation and destruction of the endothelium and of the entire vessel wall. Alternatively, embolic material may lodge in the vasa vasorum of the artery, leading to inflammation in the adventitia and muscularis, and eventually to aneurysmal dilatation.[5] An immunoallergic response to bacterial antigen may be involved in some instances of such vasculitides.[6] The reported incidence of mycotic aneurysms varies; in Pruitt's series it was proved in 1.86% and presumed in 2.8%.[5]

Septic aneurysm most commonly and most dangerously affects the cerebral vessels.[7] The associated mortality rate is extremely high,[5] although appropriate therapy may result in healing and thus avoid the need for surgical intervention prior to rupture.[5] Mycotic aneurysms were not actually seen in the central nervous system in our patient; however, their presence elsewhere in the body assures us of their presence in the central nervous system.

As was true in this case, while blood cultures are usually positive in endocarditis, the cerebrospinal fluid cultures are commonly negative in infections due to streptococci[5]; meningitis is rare.[2]

Musculoskeletal complications are of interest in bacterial endocarditis. In our patient, we found only mild osteoporosis in the vertebrae, but no evidence of emboli, vertebral or paravertebral abscess formation, or multiple myeloma.

According to Churchill et al,[8] musculoskeletal symptoms occur in as many as 44% of patients with bacterial endocarditis; in 27% they can be the first or among the first symptoms, as was the case here. The complaints include those of arthritis, arthralgia, myalgia, or low back pain and may develop at any age. They are commonly present for two to three months prior to the diagnosis of bacterial endocarditis and may improve with antibiotic therapy. They may be related to immunologic processes or to small arterial and arteriolar emboli which may contain immune complexes.[8]

Backache, which occurs in 23%, may be secondary to embolization of vertebral vessels or to involvement of disk spaces by aseptic necrosis.[2] It may be severe and be the most prominent symptom, as was the case here; it may be aggravated by straight-leg raising; and can persist, with an average duration of 1.5 months.[8]

Diffuse myalgias, on the other hand, are seen in 19% of patients, and may be localized to the thighs and calves.[8] Their cause is unknown but again they may be related to microembolism. Arterial occlusion and thrombophlebitis are not commonly found. One cannot deny that the osteoporosis and vertebral compression appear to have been the most likely causes of this patient's back pain. However, the timing of its onset, its duration, and other characteristics which I mentioned, raise the question of bacterial endocarditis as its cause, or at least as a major contributing factor.

A few other points relevant to this patient deserve mention. Endocarditis is reported to be more frequent in older people[7]; about 60% of patients are over 50 years of age and one third are 65 years or older. The clinical features are more likely to be atypical than in younger patients, and may present diagnostic difficulties—an observation also noted by Osler.[4] Many of the older patients have no evidence of antecedent heart disease,[4,7] as was true in the current case. *Streptococcus viridans* is most often the cause of bacterial endocarditis in older patients[9]; infection with this organism is associated with an average delay in diagnosis of 9.5 weeks.[7] The delay gives a chance for the vegetation to grow, to perforate the valve, and to lead to serious and often fatal complications. Although *S. viridans* is less virulent than *Staphylococcus aureus* or fungi, the course of endocarditis due to *S. viridans* can be unpredictable in the individual patient.[10]

Congestive heart failure, while rare in the young patient,[11] may occur in as high as 64% of elderly individuals with endocarditis.[9,10] Congestive failure may be secondary to valve dysfunction, perforation of a valve leaflet,[7] rupture of chordae tendineae, or myocardial damage from abscess formation.[7] Heart failure is uncommon in the early stages of bacterial endocarditis but can occur in approximately one fourth of the patients at the time of admission or within the two weeks prior to admission to the hospital.[7] It is one of the commonest causes of death in infective endocarditis, by itself or with the additional complication of cerebral emboli.[11] It very often does not respond, or responds poorly, to medical treatment[2]; and there has been no decrease in the incidence of this complication in the antibiotic era.[11]

To recapitulate: This 68-year-old woman had a history of excessive consumption of alcohol; and despite the complete absence of any of alcoholism's pathologic stigmata at autopsy, the patient may have been predisposed by alcoholism to the development of bacterial endocarditis. Osler believed that "persons addicted to drink seem particularly liable to be attacked."[4] The endocarditis developed on an otherwise normal valve and caused its perforation. This patient went on to develop congestive heart failure, embolisms to the central nervous system and to other organs, as well as abscess formation, vasculitis, mycotic aneurysms, and arterial rupture. Five days of intensive antibiotic therapy could not turn events in the patient's favor.

The chief lesson to remember here is that musculoskeletal or central nervous system findings, in the presence of a heart murmur, should arouse suspicion of infective endocarditis in middle-aged or elderly patients. This entire spectrum of complications of bacterial endocarditis is infrequently seen in modern times because of the usually early diagnosis and effective treatment. However, in cases such as the one presented today, the overall mortality remains unchanged from what it was in the past. Osler's statement of 100 years ago still holds true: "The protean character of the malady, the latency of the cardiac symptoms, and the close simulation of other disorders, combine to render the detection particularly difficult."[4]

Irwin Sharkey, MD: Could you be sure that a mycotic aneurysm was responsible for the intracranial hemorrhage, rather than a berry aneurysm?

Dr Abunassar: There was no gross evidence of berry aneurysm in the circle of Willis where they most commonly occur and where they rupture; and there was no accumulation of blood at the base of the brain, at the common site of such a rupture. In the circumstances of this patient, a subarachnoid hemorrhage on the surface of the brain would most probably represent the progression of a necrotizing vasculitis to the stage of mycotic aneurysm formation and finally to rupture.

Harold H. Coppersmith, MD (Attending Physician): A good, generally reliable clue to the presence of endocarditis is the finding of a characteristic high-pitched musical murmur, due to valve leaflet perforation.

Ira Schulman, MD (Associate Attending in Cardiology): It is all too easy to label a patient as an alcoholic, and then blame many symptoms and findings on that impression. The major elements in this patient's rapidly deteriorating course were predominantly neurologic; but at the time, I could not help but be impressed at the bedside by all the clinical features that pointed to bacterial endocarditis.

FINAL ANATOMIC DIAGNOSES

1. Bacterial endocarditis (alpha hemolytic *Streptococcus* group) involving the mitral value, with perforation of valve leaflet.
    a. Generalized sepsis.
    b. Widespread focal microscopic emboli.
    c. Focal necrotizing vasculitis.
    d. Recent embolic infarctions of kidneys and spleen.
    e. Multiple cardiac and cerebral microabscesses.
    f. Recent subdural and subarachnoid hemorrhage in region of right temporal and occipital lobes.
    g. Hematoma in left pleural cavity.
    h. Focal and segmental endocapillary and extracapillary glomerulonephritis.
    i. Chronic passive congestion and cardiac sclerosis of the liver.
2. Recent hemorrhagic infarction of left lung, secondary to pulmonary embolism.

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Edward Siegel, MD

All-American EVP

In compiling a list of the accomplishments of Edward Siegel, MD, who retired last month as executive vice-president of the Medical Society of the State of New York, one soon discovers it would be far easier to list the few things he has *not* yet achieved. "He has always been a leader and always will be a leader," observes Aaron Feder, MD, who has remained a close friend since the two roomed together in medical school at the University of Maryland where Ed Siegel was president of his fraternity, cadet colonel of the ROTC, and an all-American lacrosse player.

An eminent ophthalmologist, Dr Siegel was coauthor with Conrad Berens, MD of an encyclopedia of ophthalmology. After serving as a colonel in the United States Army Medical Corps, Dr Siegel established a practice in Plattsburgh, NY, where he became active in medical society affairs, rising to the presidency of the Clinton County Medical Society. In 1972 he was elected president of MSSNY.

"Although Ed has made his niche in soldiering and science, his basic fiber is that of the consummate politician and master tactician," notes Dr Feder. "He is an innovator who can also effect compromose. He is a patriot, a soldier, and a man for all seasons."

AB

Trimethoprim–sulfamethoxazole-related hypoglycemia in a patient with renal failure

MATTHEW C. FRANKEL, MD, BRUCE R. LESLIE, MD, FREDERIC L. SAX, MD, ROSEMARY SOAVE, MD

Hypoglycemia has been reported as a side effect of a variety of medications.[1] Patients with chronic renal failure are at increased risk of developing drug-induced hypoglycemia, owing in part to alterations in drug metabolism.[2] We report a patient with end stage renal disease who developed severe hypoglycemia while receiving large doses of trimethoprim-sulfamethoxazole (Bactrim; Roche Laboratories, Division of Hoffmann-La Roche, Inc, Nutley, NJ).

CASE REPORT

A 63-year-old patient with end stage renal failure secondary to chronic glomerulonephritis, for which he had received hemodialysis, presented with pyogenic arthritis of the right wrist. On admission, the patient appeared well nourished; the weight was 63 kg, height, 184 cm. The serum glucose level was 120 mg/dL; the creatinine value was 11 mg/dL. Electrolytes and liver function test results were within normal limits. There was no history or family history of diabetes mellitus. Medications on admission were aluminum hydroxide, multivitamins, and folic acid.

Culture of a right wrist aspirate grew methicillin-resistant *Staphylococcus aureus*, sensitive only to vancomycin (minimum inhibitory concentration: 25 μg/mL) and trimethoprim (MIC: 0.125 μg/mL). Vancomycin was contraindicated due to a previous exfoliative dermatitis when exposed to this drug. Because it was feared that the organism would develop resistance to trimethoprim if used alone, the patient was given the combination of 160 mg trimethoprim-800 mg sulfamethoxazole (Bactrim DS), three tablets orally twice daily. Peak serum trimethoprim and sulfamethoxazole levels one and one half hours after a dose were 15 μg/mL and 72 mg/dL, respectively. Daily morning serum glucose levels ranged between 110 and 135 mg/dL. Five days after beginning therapy, the patient had a grand mal seizure. The serum glucose was 26 mg/dL. Intravenous glucose was administered and seizure activity ceased. A repeated glucose determination the next morning (while still receiving intravenous glucose) was 121 mg/dL.

The following day, the glucose infusion was stopped and three tablets of trimethoprim-sulfamethoxazole were administered. One and one half hours later, the serum glucose was 75 mg/dL. A simultaneous serum insulin level was 58.7 μIU/mL (normal, 6 to 26 μIU/mL). Three hours after the dose, the serum glucose had decreased to 50 mg/dL, and symptoms of hypoglycemia necessitated reinstitution of the glucose infusion. The eighth day, both intravenous glucose and trimethoprim-sulfamethoxazole were omitted. A serum glucose measured one and one half hours after the scheduled antibiotic dosage time was 135 mg/mL.

Additional determinations included normal thyroid function tests (T3, T4, and thyroid-stimulating hormone), normal morning ACTH and growth hormone levels, normal diurnal cortisol levels, and a normal alanine level (thin layer chromatography). At a time when the patient was relatively hypoglycemic (65 mg/dL) following trimethoprim-sulfamethoxazole ingestion, the insulin C-peptide value was 10 ng/mL (normal, 0.7 to 3.3 ng/mL) and the glucagon level was 949 pg/mL (normal, 25 to 175 pg/mL).

The patient's antibiotic regimen was changed to one tablet of Bactrim DS with 100 mg of trimethoprim, twice daily. On this dosage, peak trimethoprim and sulfamethoxazole levels were 8.6 μg/mL and 33.4 mg/dL, respectively. Hypoglycemia did not recur. After discharge, on the same antibiotic regimen, following a 14-hour fast, the serum glucose level was 131 mg/dL with a simultaneous insulin level of 22 μIU/mL. Although a formal glucose tolerance test was not performed, repeated glucose determinations as an outpatient were persistently within normal range. The patient eventually required readmission and surgical debridement of the right wrist. Specimens revealed necrotic bone and abscesses which grew the same resistant *S. aureus*.

DISCUSSION

Spontaneous hypoglycemia in patients with chronic renal failure both with and without diabetes has been previously reported.[3-6] The proposed mechanisms for this occurrence include: deficiency of the substrates for gluconeogenesis, eg, alanine, due to either dietary insufficiency or losses via hemodialysis[7]; impaired hepatic gluconeogenesis[2]; and delayed catabolism of endogenous insulin.[4] Despite the impairment in insulin degradation in uremia, plasma insulin response to hypoglycemia has been normal in five out of five cases.[3,5,6] Our patient, however, had inappropriately high plasma concentrations of insulin and C-peptide when relatively hypoglycemic. This is consistent with either decreased insulin catabolism or increased endogenous insulin release.

Sulfamethoxazole bears a strong chemical resemblance to the oral hypoglycemic sulfonylureas. In fact, the sulfonylureas were developed following the observation that a sulfonamide antibiotic reduced serum glucose levels.[8] Cohen et al[2] have shown that the response to sulfonylureas in uremic patients is delayed and exaggerated. Once established, the hypoglycemia may become prolonged and refractory due to delayed excretion of the drug, with continuous stimulation of the pancreas to release insulin. Sulfonamides have been reported to potentiate the action of sulfonylureas, presumably by displacing them from their serum protein binding sites or by altering their metabolism.[9] Severe hypoglycemia associated with sulfamethoxazole therapy alone has not been previously reported. (*See Addendum*) While an insulin-secreting tumor could also account for this clinical picture, this was thought

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From the Rogosin Kidney Center (Drs Frankel, Leslie) and the Department of Medicine (Drs Sax, Soave), The New York Hospital-Cornell Medical Center, New York City

Address correspondence to Dr Frankel, Fellow, The Rogosin Kidney Center, The New York Hospital-Cornell Medical Center, 525 East 68th St, New York, NY 10021.

to be less likely in view of the close temporal relationship between administration of trimethoprim-sulfamethoxazole and hypoglycemia, the elimination of hypoglycemic episodes when the dose of sulfamethoxazole was reduced, and the normal glucose and insulin levels after a prolonged fast.

Systematic timed observations following drug rechallenge may have proved a cause-and-effect relationship between sulfamethoxazole and hypoglycemia. This was felt to be ethically unjustifiable, however, in view of the potentially serious side effect. Nevertheless, sulfamethoxazole administration was temporally associated with symptomatic hypoglycemia, and reduction of the dose of this agent alone eliminated this phenomenon. The data presented are consistent with the hypothesis that sulfamethoxazole stimulated pancreatic insulin release, resulting in symptomatic hypoglycemia with an inappropriately high insulin level. This may have occurred as a consequence of the administration of large doses of sulfamethoxazole to a patient with renal failure, in whom drug metabolism is impaired. As the therapeutic indications for trimethoprim-sulfamethoxazole increase, it is suggested that blood glucose levels be monitored in patients with chronic renal disease receiving this agent.

ADDENDUM

Since the submission of this manuscript, an additional report of trimethoprim-sulfamethoxazole-related hypoglycemia has appeared.[10] Although the patient presented in the present report was treated with a larger drug dosage (4,800 mg of sulfamethoxazole per day, compared with 1,600 mg sulfamethoxazole per day), the data are nonetheless in agreement. Both reports demonstrate inappropriately elevated insulin levels with concomitant hypoglycemia in patients with chronic renal failure. Both reports incriminate the sulfonamide moiety in trimethoprim-sulfamethoxazole as the agent responsible for this occurrence.

Acknowledgments. The authors wish to thank Athanasia Apostolopoulos, MD, of The New York Hospital-Cornell Medical Center, Connie Mussenden of Rogosin Kidney Center, and Hoffman-La Roche, Inc for their professional and technical assistance.

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Pancreatic cholera

HARRY JACKSON, MD, SIDNEY GLASSBERG, MD

Pancreatic cholera, also known as the Verner-Morrison syndrome or the WDHA syndrome (watery diarrhea, hypokalemia, and achlorhydria), was initially thought to be a variant of the Zollinger-Ellison syndrome. Since the description by Zollinger and Ellison[1] in 1955 of two cases of recurrent jejunal ulcer associated with gastric hyperacidity and hypersecretion, subsequent case reports confirmed the association between non-insulin-secreting islet cell tumors and the Zollinger-Ellison syndrome.

Verner and Morrison[2] in 1958 described a syndrome of profuse watery diarrhea and severe hypokalemia associated with islet cell tumors of the pancreas, and unassociated with ulcers.

The case we describe here fulfills the criteria outlined by Verner and Morrison.

The dominant symptom, cholera-like diarrhea, is often present for three to four years, with volumes that may exceed 6 to 8 L of stool in 24 hours. The stools may look like diluted tea and contain an average excretion of 300 mEq of potassium in 24 hours. The normal 24-hour excretion of potassium in stool is 9 mEq.[3] Correction of hypokalemia with intravenous potassium may require massive infusions. The other manifestations in over half the patients include basal gastric achlorhydria, steroid responsiveness, diabetes mellitus, and hypercalcemia.

CASE REPORT

A 59-year-old man was admitted electively to LaGuardia Hospital for evaluation of painless diarrhea of five months' duration. At the time of admission he was having watery, foul-smelling, orange stools with 10 to 12 movements per day, in addition to sporadic episodes of explosive diarrhea. He was known to have diabetes mellitus for nine years, which was treated with chlorpropamide (Diabinese) until one year before admission. At that time, he was placed on 30 units NPH insulin, because his diabetic status had apparently worsened. He had been impotent for one year prior to admission, and had suffered a myocardial infarction at age 54. Physical examination was within normal limits. Results of sigmoidoscopy and barium enema were negative. Upper gastrointestinal series with small-bowel series showed some puddling of barium, consistent with increased secretions. Fat content of stool was normal. The patient was discharged on a regimen of tetracycline and diphenoxylate (Lomotil). However, the

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From the Departments of Medicine (Dr Jackson, Attending in Gastroenterology) and Pathology (Dr Glassberg), LaGuardia Hospital, Forest Hills, Queens, NY

Address correspondence to Dr Jackson, 25–31 30th Road, Astoria, NY 11102.

diarrhea persisted, and five months after discharge from the hospital, the potassium level was noted to be 2.9 mEq/L. Management was attempted with supplementary potassium for the next six months but was becoming increasingly difficult, and the patient was referred for consultation. He was then readmitted to LaGuardia Hospital 16 months after his first admission. The patient did not appear in acute distress and results of physical examination were within normal limits. Urine values were within normal limits.

Laboratory studies disclosed the following values: hematocrit, 46%; WBC, 6,400 with 67 neutrophils, 32 lymphocytes, and 1 monocyte; blood glucose, 220 mg/dL; BUN, 20 mg/dL; cholesterol, 140 mg/dL; total protein, 6.2 mg/dL (albumin, 3.8, globulin 2.4). Bilirubin content was 0.5 mg/dL; alkaline phosphatase, 225 IU; lactic dehydrogenase, 140 U/mL; SGOT, 35 U/mL. Electrolyte values were potassium, 2.2 mEq/L; sodium, 136 mEq/L; chloride, 106 mEq/L; bicarbonate, 22 mEq/L. The serum lipase content was 0.5 U; amylase, 111 U/dL. Results of stool examination for fat were negative. Urine hormone values were: 17-ketosteroids, 10.5 mg; 17-hydroxysteroids, 10.3 mg; and 5-hydroxyindoleacetic acid, 3.1 mg in a 24-hour urine collection. Serum aldosterone was 501 μg/dL; serum cortisone, 18 μg/dL; serum T_3, 32%; T_4, 9 μg/dL.

Results of liver scan and intravenous pyelography were normal. Results of upper gastrointestinal series and small-bowel series were normal, except that the jejunum showed evidence of increased secretion. Results of barium enema examination were normal. The histamine stimulation test (Histalog, Eli Lilly) was performed and basal gastric acidity was 0. After the histamine injection, free hydrochloric acid was still 0.

The patient was producing approximately 2 L of watery fecal material per day. A specimen of stool contained more than 1,000 mEq potassium per liter. Intravenous potassium was given and his serum potassium level slowly rose to 2.8 mEq/L. Prednisone therapy, 20 mg daily, was started and the volume of diarrhea went from 2 L to 800 cc per day. The patient was transferred to Mount Sinai Hospital, New York City, for arteriography. After gastroscopy, colonoscopy, and small-bowel biopsy were performed with negative results, superior mesenteric arteriography showed a 6 × 7-cm mass in the left upper quadrant, within the pancreas (Fig 1).

Blood samples were sent to the laboratory of S. I. Said, MD in Dallas, Texas to be tested for vasoactive intestinal polypeptide (VIP). The preoperative values in three samples were 760, 660, and 550 pg/mL (normal VIP values, 19 to 143 pg/mL).

The patient underwent a distal pancreatectomy and splenectomy. A circumscribed, solid pancreatic tumor measuring 6 cm was found (Fig 2). Microscopy revealed an endocrine neoplasm of islet cell–carcinoid type, composed of cords and nests of regular cells with minimal mitotic activity (Fig 3). No evidence of vascular invasion was found. Stains for beta granules and argentaffin stain were negative.

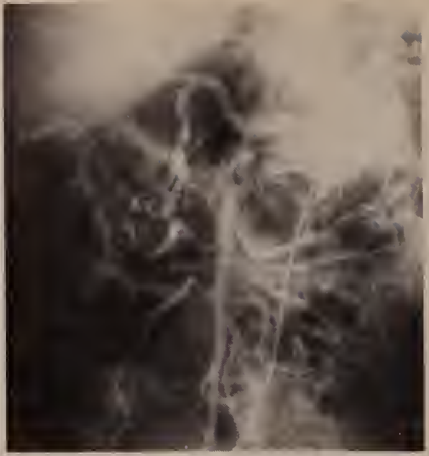

FIGURE 1. Superior mesenteric arteriogram shows 6 × 7-cm vascular mass in left upper quadrant, within pancreas.

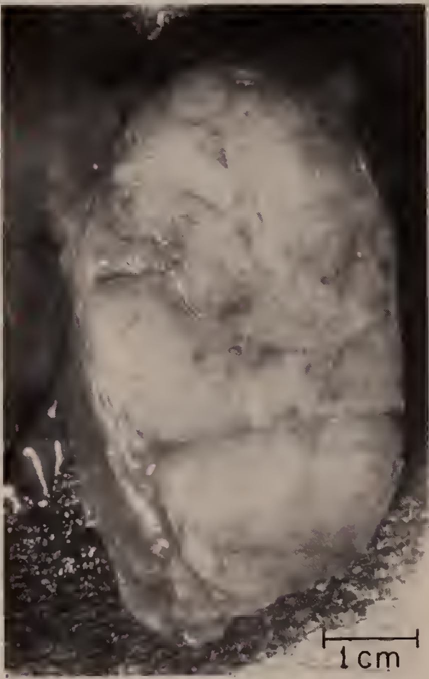

FIGURE 2. Solid pancreatic tumor measuring 6 cm.

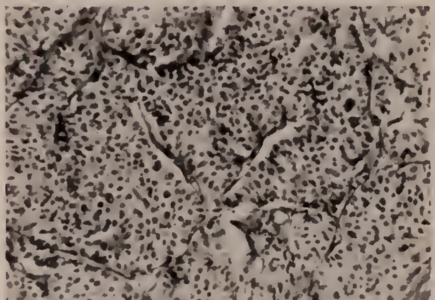

FIGURE 3. Endocrine neoplasm of islet cell–carcinoid type composed of cords and nests of regular cells with minimal mitotic activity.

VIP levels of all three blood samples drawn on the first day after operation were 50 pg/mL. Bioanalysis of tumor tissue showed it to be rich in VIP, with a content of 30 ng/g, following 1:20 dilution of tissue extract. Normal values in rabbit pancreas are 60 ng/mL, undiluted.[4] Prostaglandin E and human pancreatic polypeptide were not measured.

The patient's symptoms cleared and he was discharged from the hospital one month after the operation.

DISCUSSION

The polypeptide-secreting tumors responsible for pancreatic cholera are composed of specialized cells which form a miscellaneous group. These cells are situated, for the most part, in the intestine and in the derivatives of the embryonic foregut. They are specialized for the production of polypeptides and amines. The word frequently used for tumors of these cells is "apudoma," from APUD, which is an acronym derived from *a*mine *p*recursor *u*ptake (of such amines as dopa or 5-hydroxytryptophan) and *d*ecarboxylation. APUD cells were found to have structural and chemical similarities to ganglion cells and other central nervous system cells. In the embryo, it was found that the neuroectodermal cells of the neural crest displayed APUD characteristics and could be shown to invade the foregut and its derivatives. These cells probably originally represented a primitive nervous system. The actions of many adjacent APUD cells appear to have antagonistic qualities, which may represent local feedback systems controlling some of the functions of the gastrointestinal tract.

Apudomas may secrete more than one polypeptide or such substances as prostaglandins, histamines, and others. Some apudomas may be part of the syndrome of multiple endocrine adenopathy (MEA). In MEA-I, a pancreatic islet cell tumor is associated with a pituitary tumor and hyperparathyroidism. For this reason, one should search for other substances which may be associated with the WDHA syndrome, such as gastrin, calcitonin, catecholamines, and serotonin.[5]

Since the discovery of the syndrome of pancreatic cholera, the search for the agent causing the symptoms has continued until the present. In 1969, Tompkins et al,[6] as well as others, attempted to demonstrate that the diarrheogenic effect was produced by a secretin-like hormone.

Prostaglandins (a group of long-chain

unsaturated oxygenated fatty acids discovered in 1933 by Goldblatt[7] in semen and seminal vesicles) were found to stimulate smooth muscle, and later some prostaglandins were found to be potent inhibitors of gastric secretion.[8] In a patient described by Jaffe et al,[9] increased peripheral plasma levels of prostaglandin E returned to normal after resection of a pancreatic tumor. Administration of indomethacin, a potent inhibitor of prostaglandin biosynthesis, caused the diarrhea and hyperglycemia to cease.

Another possible mediator in the WDHA syndrome may be human pancreatic polypeptide (HPP). Polak et al[10] described that in the course of purifying glucagon and insulin, Lin and Chance extracted bovine pancreatic polypeptide, which had previously only been described in birds. It was found to stimulate bicarbonate production and to inhibit gallbladder tone in dogs. In 1976 Floyd and Fajans[11] described human pancreatic polypeptide in islet cells and scattered in exocrine pancreas. They showed that basal plasma levels might be elevated in functioning and nonfunctioning islet cell tumors. In 1976 Larsson et al[12] examined 18 endocrine pancreatic tumors for the occurrence of cells producing HPP. More than half of the tumors were mixed, containing more than one type of hormone-producing cell. Three of four tumors causing the watery diarrhea syndrome contained both VIP and HPP cells. In one such tumor, there was a strong predominance of HPP cells. The patient's serum HPP levels were a thousandfold elevated, whereas her VIP levels were within the normal range.

In 1970 vasoactive intestinal peptide was isolated from the upper small intestine of pigs by Said and Mutt,[13] and in 1973 Bloom et al[14] described six patients with the watery diarrhea syndrome who were found to have raised plasma levels of VIP. Morrison and Verner[15] reviewed 54 cases of hyperplasia of nonbeta islet tissue in 1974. Of the 54 patients, 37% had benign neoplasms and were cured by surgery, while 13% had diffuse hyperplasia of the nonbeta islet tissue. In another series of 30 patients with chronic watery diarrhea studied by Said and Faloona, VIP was measured by radioimmunoassay. Twenty-eight of the 30 patients had elevated levels of VIP in plasma or tissue, or both. Thirteen patients had pancreatic islet cell adenomas, four had islet cell hyperplasia, five had bronchogenic carcinoma, and one each had pheochromocytoma and ganglioneuroblastoma. As Jaffe[16] has stated, despite the frequency of elevated VIP levels, not all patients with the WDHA syndrome have increased plasma levels of VIP. Other hormones, already known or not yet discovered, may be causing the symptoms of watery diarrhea. As an example, he cites the VIP-like peptide PIHA (porcine-intestine-histadine-isoleucine-amide), isolated by Mutt and his coworkers, which stimulates the release of cyclic adenosine monophosphate (cAMP), as does VIP. Therefore, although VIP has been implicated as the agent responsible for symptoms of the WDHA syndrome, it appears that other hormones cannot be excluded as mediators.

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Aortocoronary paraganglioma

Anatomic relationship of left coronary artery to paraganglia of aorta

HARRY H. ORENSTEIN, MD, GEORGE E. GREEN, MD, PUSHPA L. KANCHERLA, MD

Aortocoronary paraganglioma is a rare neoplasm of the heart arising from paraganglia located on the left side of the aorta and involving the coronary vessels secondarily. Five paragangliomas of the heart have been reported, all located in regions other than the aortocoronary area.[1-5]

The tissue is derived from neural crest and neural ridge components.[6-8] Classified by Pearse[9] in the *a*mine *p*recursor *u*ptake and *d*ecarboxylation (APUD) series of tumors, it possesses neuroendocrine potential of synthesizing multiple peptides and polypeptides. This tissue receives its blood supply from the intertruncal artery, a constant microanatomic branch of the left coronary artery.

From the Surgical Service, Division of Cardiovascular Surgery, and the Department of Pathology, St. Luke's-Roosevelt Hospital Center, New York City

Address correspondence to Dr Orenstein, 212 East 30th Street, New York, NY 10016.

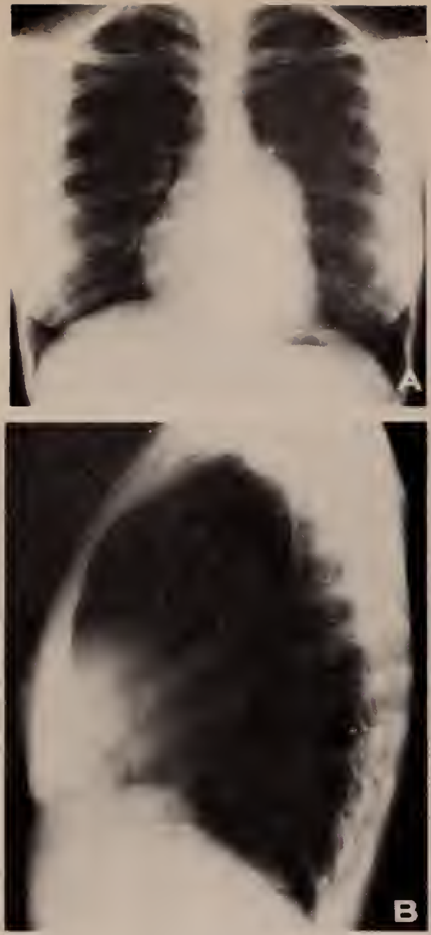

FIGURE 1. (A) Posteroanterior view of presenting chest roentgenogram. Note enlarged upper left heart border with elevation of pulmonary vessels. (B) Lateral view showing loss of retrosternal space due to tumor.

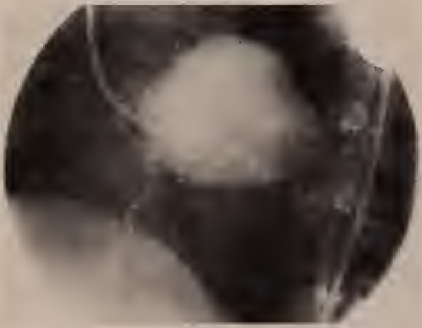

FIGURE 2. Preoperative left anterior oblique coronary arteriogram of left main stem ostia showing tumor blush. Initial diagnosis was arteriovenous malformation.

CASE REPORT

A 27-year-old woman was admitted to the cardiovascular surgery service, St. Luke's Division, St. Luke's-Roosevelt Hospital Center for surgical treatment of a mass, thought to be an arteriovenous malformation of the left coronary artery. This mass was first noted on chest roentgenogram (Fig 1) and further defined by cardiac angiography (Fig 2). The patient developed angina that was progressive despite intensive medication with propranolol hydrochloride and isosorbide dinitrate.

Physical examination revealed a normotensive patient without hoarseness or neck masses. No cardiac thrills or heaves were present. There was a grade 3/4 systolic and diastolic murmur throughout the entire cycle diminishing at end diastole, heard loudest in the pulmonic area, radiating down the left sternal border, and heard faintly in the left supraclavicular area. The intensity of the murmur increased with expiration.

Past medical history was significant for bilateral hearing deficits since age 15 years. Computerized axial tomography of the head showed bilateral otosclerosis. Results of blood and urine studies were normal. Family history was noncontributory.

At time of operation, the mass was entirely beneath the epicardium, measured 12 cm in diameter, had a prominent thrill, and was of a dense consistency. It totally encompassed the left main coronary artery and the proximal portion of the anterior descending and circumflex arteries. The mass was judged to be unresectable. Saphenous vein grafts were placed from the lateral trunk of the circumflex artery to the aorta and from the left anterior descending artery to the aorta. The left main coronary artery was sutured closed from inside the aorta with a continuous suture of prolene. The mass was then oversewn with multiple mattress sutures tied over pledgets of Teflon felt until the thrill in the mass was obliterated. The patient tolerated the procedure well and there were no complications. The murmur was not present at discharge, but did recur one month following operation. Three months following operation, mild angina recurred, but has been well-controlled with propranolol.

Pathologic findings. The 1.5 × 0.5 cm biopsy specimen from the tumor was firm and had a pale tan cut surface. Microscopically, it was composed of organized nests of polyhedral epithelial cells separated by a rich network of small blood vessels (Fig 3). The epithelial cells contained regular ovoid nuclei with punctate nucleoli and no mitoses. Both argentaffin and argyrophilic granules were discernible in the special stains (Masson, Fontana's, and Grimelius stains). By electron microscopy, many tumor cells contained intracytoplasmic granules (Fig 4).

DISCUSSION

Kohn in 1900[10] defined paraganglia as collections of neuroepithelial cells similar in character to the chromaffin tissue of the adrenal medulla and associated with sympathetic ganglia. This designation developed from his investigation of the carotid paraganglia which he termed "paraganglia intercaroticum." Mulligan[11] coined the term chemodectoma to classify neoplasms consisting of chemoreceptor cells, associated with the distribution of parasympathetic nerves, and occurring along branches or in ganglia of the glossopharyngeal and vagus nerves. As the common embryology, ultrastructural histology, and neuroendocrine potential of sympathetic and parasympathetic tumors became evident, Grimley and Glenner[12] proposed the term paraganglioma be used together with a topographic designation. Pearse[9] incorporated paraganglia into the APUD group of tumors which are related by shared cytochemical and ultrastructural features, indicating a

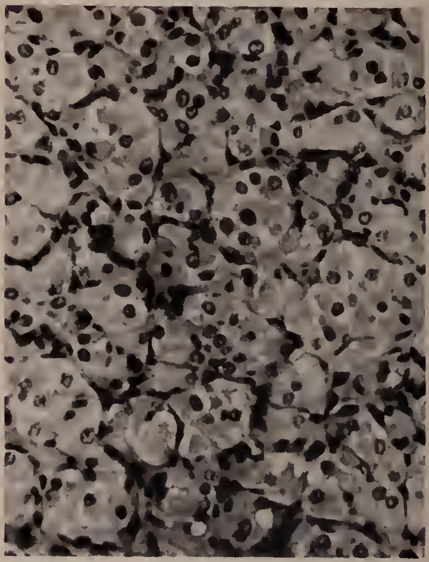

FIGURE 3. Light microscopic picture of tumor demonstrating characteristic organized nests of polyhedral epithelial cells separated by rich network of small blood vessels (hematoxolin and eosin, original magnification ×400, moderately reduced).

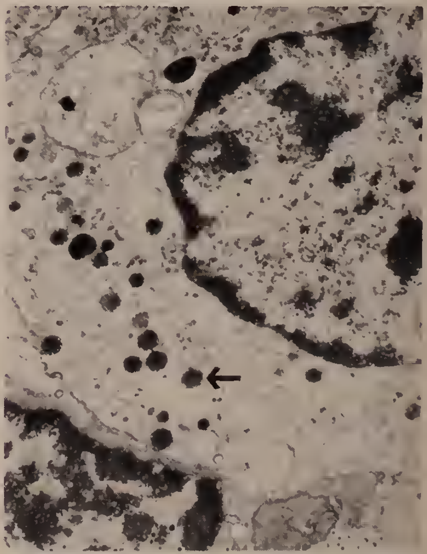

FIGURE 4. Transmission electron micrograph illustrating multiple dark-staining neurosecretory intracytoplasmic granules (×10,000).

Summary of Cardiac Paragangliomas

Case No.	Author	Sex	Age	Anatomic Site	Presentation
1	Barrie[1]	M	63	Pericardium over right atrium	Autopsy
2	Davies and Randall[2]	F	67	Parietal pericardium, right atrium	Autopsy
3	Delfante and Watkins[3]	M	51	Left atrium	Chest roentgenogram
4	Gopalakrishnan et al[4]	F	47	Left ventricle	Chest roentgenogram
5	Roujeau and Cornu[5]	M	57	Right ventricle	Autopsy
6	Orenstein et al	F	27	Aorticocoronary region	Chest roentgenogram

neuroendocrine function and an origin from migratory neural crest cells. APUD system cells are pluripotential before migration. The environment in which the cells come to rest determines their differentiation. Paragangliomas have been reported that secreted catecholamines, calcitonin, and adrenocorticotrophic hormone.[7]

Diverse microparaganglia have been described throughout the heart, and especially along the posterior wall of both atria and coronary sinus.[13,14] Wiesel in 1906[15] first described paraganglia of the aortocoronary region, noting a body of chromaffin tissue appearing like an elongated lymph node, topographically related to the left coronary artery. Survey of the literature revealed five case reports of cardiac paraganglioma (Table).

The microvascular supply to the aortocoronary paraganglia is a constant anatomic structure. Boyd[16] identified paraganglia in fetal specimens 50 to 60 days of age, noting direct vascularization from a branch of the pulmonary trunk. In fetal life this pulmonary branch becomes obliterated and the intertruncal artery, a branch of the left coronary artery, becomes the source of vascular supply. Becker[17] verified this sequence and identified occasional obliterated remnants from the pulmonary trunk. The vasa vasorum for both aorta and pulmonary trunk originate from the intertruncal artery. Nerves, lymph nodes, and adipose tissue also receive flow from this branch. The intertruncal artery has specific morphologic characteristics particular to pressor-sensing vessels which were described by DeCastro[18] in the carotid sinus, a known pressoreceptor, as a change in the medial coat from smooth muscle to elastic fibers arranged in concentric laminae. This change occurs along the intertruncal artery at the region of the paraganglia.[14,17]

Although most paragangliomas are slow-growing, benign tumors, the incidence of malignancy is approximately 10%. The age spectrum ranges from 18 to 78 years.[19] Angiography has been the most accurate diagnostic test.[20] Carotid paragangliomas have a pathognomonic picture of a separation of the internal and external carotids by a highly vascular circumscribed mass.[20,21] The angiographic description of our tumor was similar to the one reported by Gopalakrishnan et al.[4] In both cases a highly vascular mass encompassed blood vessels and appeared like an arteriovenous malformation. Strong family histories suggest a genetic etiology.

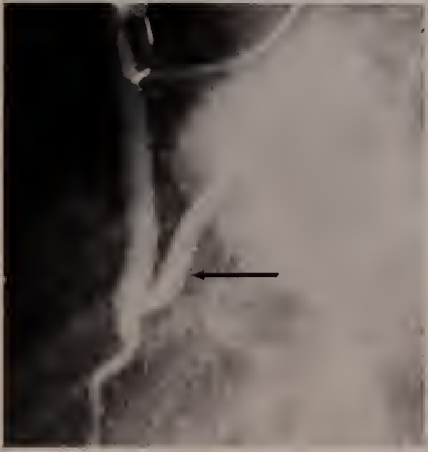
FIGURE 5. Postoperative left anterior oblique coronary arteriogram of saphenous vein graft from proximal aorta (short arrow) to midportion of anterior descending artery displays normal distal half and large, hypertrophied proximal segment (long arrow). There is retrograde flow entering tumor mass. This retrograde filling also occurred in bypass graft of lateral branch of circumflex system, despite obliteration of the communication at operation as judged by elimination of bleeding from cut surface and elimination of palpable thrill.

Radiation therapy in malignant paragangliomas has not been effective and chemotherapeutic trials have not had good results.[19]

In this patient the mass was not resectable. Obliteration was attempted by oversewing the mass and closing its inflow from the left main coronary artery. Saphenous vein bypass grafts to the left anterior descending and circumflex arteries maintained distal perfusion. The murmur recurred one month after operation and angina three months after operation. Repeat angiography six months after operation demonstrated wide patency of both vein grafts, but they perfused the tumor as well as the normal myocardium (Fig 5). Furthermore, suture of the left main coronary ostium had not completely obliterated communication from the aorta to the left main coronary artery (Fig 6).

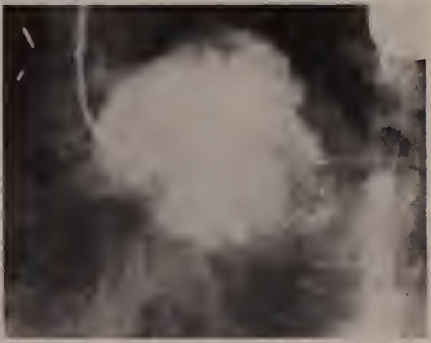
FIGURE 6. Postoperative left anterior oblique coronary arteriogram of left main stem ostia again showing tumor blush. Ostium was sutured closed at operation and became patent with return of murmur and angina.

Newer methods appear to be necessary for successful treatment of this tumor. Embolotherapy could be attempted but is unlikely to be capable of obliterating the tumor.[22] Argon laser therapy has been used with moderate success for capillary hemangiomas[23] and should be considered. Finally, heart transplantation may be the ultimate recourse.

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Functioning tumor of the organ of Zuckerkandl

VIDYADHARA A. KAGALI, MD, M. ALI MADANI, MD, SOMSAK BHITIYAKUL, MD,
HANS H. MULLER, MD

Catecholamine-producing tumors may be found wherever paraganglion tissue exists, and they may be associated with multiple endocrine neoplasia. About 10% of pheochromocytomas are extra-adrenal.[1] Adrenal and extra-adrenal pheochromocytomas continue to evoke interest, because they possess the unique combination of being potentially lethal, yet benign and curable in about 90% of patients.[2] The tumor is rare with incidence ranging from 0.01% to 0.1% of the hypertensive population in the United States.[2] Since follow-up of patients with successful excision of tumor of the organ of Zuckerkandl is not as well documented as those of pheochromocytomas of adrenal origin, there is a need for reporting such cases.[3]

CASE REPORT

A 36-year-old plumber was admitted to the Kingston Hospital Intensive Care Unit in April 1982 with chief complaints of progressive weakness, shortness of breath, dizziness, and tarry stool for four days prior to admission. He also experienced frequent headaches and excessive sweating. Examination revealed an acutely distressed well developed pale white man. His pulse was 116/min and regular; BP was 150/100 mm hg. His temperature was 36.9°C (98.4°F). There was a grade 3/4 systolic murmur over the precordial region. The abdomen was soft without palpable mass. Rectal examination revealed tarry stools. Admission hemoglobin level was 8.9 g/dL with hematocrit of 26%. Clinical impression was that of upper gastrointestinal bleeding secondary to a duodenal ulcer. He was treated with cimetidine, 300 mg every six hours, and 30 mL of an antacid every two hours. His blood pressure was controlled with metoprolol tartrate (Lopressor) 50 mg daily, hydrochlorothiazide 25 mg, and triamterene 50 mg daily. He also received three units of packed red cells. The patient became acutely short of breath and dizzy within a few hours after admission, and his blood pressure rose to 210/130 mm Hg. The next day he developed another hypertensive crisis; intravenous (IV) nitroprusside, 175 μg/min, was given under constant BP monitoring. After his BP and bleeding were controlled, an upper gastrointestinal series showed a duodenal ulcer.

Twenty-four hour urine for metanephrine on the day after his hypertensive crisis was 7.6 mg (normal, 0.1 to 0.9 mg/24 h). The level of urinary catecholamines was 1,834 μg/24 h (normal, 0 to 115 μg/24 h). Serum calcitonin was 104 pg/mL (normal, 0 to 300 pg/mL.). His blood pressure was controlled with a low sodium diet, hydrochlorothiazide 25 mg/ daily, and metoprolol 50 mg twice a day. An intravenous pyelogram showed a small right kidney. Echocardiogram revealed idiopathic subaortic stenosis. His bleeding episode stopped and tests for occult blood in stool became negative. He was discharged on the ninth day.

When followed as an outpatient, he continued to show fluctuating hypertension associated with sweating and dizzy spells requiring him to be readmitted for hypertension work-up. His blood pressure fluctuated from 120/80 mm Hg to 170/108 mm Hg despite treatment with a low sodium diet, hydrochlorothiazide 25 mg daily, metoprolol 50 mg daily, and phenoxybenzamine 10 mg twice a day. An aortogram showed vascular tumor over the inferior vena cava (JVC) and the abdominal aorta overlying the right lumbar region (Fig 1). Computed tomography (CT) scan showed a 5-cm lobulated mass above the level of the aortic bifurcation (Fig 2). A diagnosis of extra-adrenal pheochromocytoma was made. On September 14, 1982 he un-

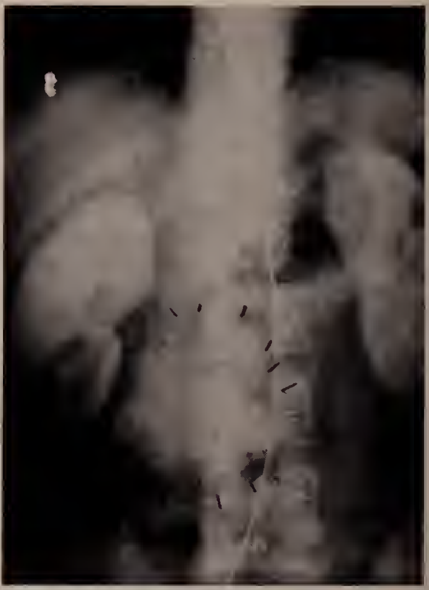

FIGURE 1. Aortogram visualizing right retroperitoneal, para-aortic mass superior to aortic bifurcation and in vicinity of inferior mesenteric artery.

From the City of Kingston Laboratory, Kingston, New York.

Address correspondance to Dr Kagali, Pathologist, City of Kingston Laboratory, 400 Broadway, Kingston, NY 12401.

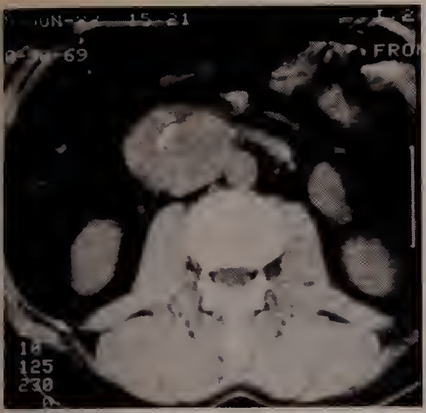

FIGURE 2. CT scan showing circumscribed 5.0-cm tumor with focal calcification in right paravertebral region.

derwent an exploratory laparotomy. Preoperative medication consisted of hydroxyzine pamoate 50 mg intramuscularly (IM). No atropine was given. On arrival in the operating room, the patient's BP was found to be 220/120 mm Hg and he received phentolamine, 2 mg IV and 3 mg IM, which lowered his BP to 150/70 mm Hg. He was then prepared for surgery by insertion of no. 14 IV catheters in both upper extremities and placement of a central venous pressure line via the right subclavian vein. The patient was induced with sodium pentothal and an endotracheal tube was placed following application of 4% topical lidocaine to his trachea and larynx under constant EKG and BP monitoring. In spite of these precautions, immediately following intubation he developed runs of bigeminy and supraventricular tachycardia which were controlled with lidocaine drip and propranolol hydrochloride, 1 mg IV. During surgery the patient's BP was controlled by nitroprusside drip at a rate of 2 μg/kg/min augmented during a few hypertensive episodes with an IV bolus of 2 to 3 mg phentolamine. On two occasions the surgeons were requested to stop handling the tissues until his BP was under control. Immediately after ligation of the tumor vessels the patient experienced an episode of hypotension which was corrected by IV infusion of metaraminol bitartrate. An 8 × 5 × 5-cm, fleshy, lobulated tumor was removed during surgery. The tumor was overlying the abdominal aorta and IVC, adjoining the origin of the inferior mesenteric artery, and encircling two thirds of the circumference of the aorta and the IVC. Further exploration of the abdomen including adrenal glands revealed no other tumor.

The tumor weighed 75 g and measured 8.0 cm in its greatest diameter. It was fleshy, lobulated, and sharply circumscribed with a thin peripheral tissue resembling that of a capsule. The cut surface was light tan with a slightly reddish hue. Under the microscope the tumor was seen to be composed of fairly uniform and slightly pleomorphic cells with prominent oval or round nuclei and granular eosinophilic cytoplasm. The cells tended to be arranged in alveolar nests in the vascular stroma (Fig 3).

His postoperative course was uneventful and he was discharged eight days after operation. He is now normotensive with no antihypertensive medication. The postoperative 24-hour urine metanephrine level was 0.3 mg (normal, 0.1 to 0.9 mg/24 h); the 24-hour urine catecholeamine level was 64 μg (normal, 0 to 115 μg/24 h).

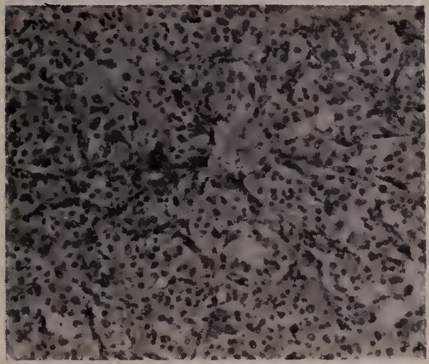

FIGURE 3. Pheochromocytoma of organ of Zuckerkandl. Note pattern of small nests of polygonal and oval cells with finely granular and homogeneous eosinophylic cytoplasm. Cells have round or oval, slightly pleomorphic hyperchromatic nuclei. (Hematoxylin and eosin, original magnification ×100.)

DISCUSSION

In 1901, the Austrian anatomist, Erich Zuckerkandl (1849–1910), described in neonates collections of paraganglion cells overlying the aorta, below the origin of the inferior mesenteric artery. Since then the area has been expanded to include collections of paraganglion cells in the lower abdominal aorta and its bifurcation.[1] The organ of Zuckerkandl is a prominent ganglion structure in the fetus and is located on the anterior surface of the abdominal aorta, most often in the neighborhood of the inferior mesenteric artery. The structure involutes by about the eighth month of fetal life. In the adult, its vestige forms a loose plexus of sympathetic fibers along the anterior surface of the lower abdominal aorta.[1,4] Pearse showed that these collections of paraganglion cells have biochemical and ultrastructural features in common with other neuroectodermal cells of neural crest origin.[5] These migrated cells have a biochemical mechanism for synthesis, storage, and secretion of biogenic amines such as dopamine, norepinephrine, epinephrine, and serotonin. Pearse labeled them APUD cells, based on their ability to form *a*mines by *p*recursor *u*ptake of polypeptides and their *d*ecarboxylation. Thus, the adrenal medulla and extra-adrenal paraganglion system form part of this APUD system. Functioning tumors arising from the adrenal medulla and extra-adrenal paraganglion system are called pheochromocytomas or "apudomas."

About 10% of pheochromocytomas are extra-adrenal.[1] In one series of 106 pheochromocytomas, the authors report the incidence of extra-adrenal pheochromocytoma to be as much as 18%.[3] This high incidence is probably due to selective referral. Extra-adrenal pheochromocytomas are more common in children (30%) than in adults (10%). The higher incidence in the pediatric age group is probably because the paraganglion system is more developed in children than in adults.[6] Consistent with this greater mass of paraganglion tissue, paragangliomas in children are frequently multiple and extra-adrenal.[7] Glenner and Grimley[1] have separated these tumors into four categories: branchiomeric, intravagal, visceral autonomic, and aorticosympathetic paraganglioma. Paragangliomas of the organ of Zuckerkandl belong to the last category. The tumors of the organ of the Zuckerkandl comprise 40% to 50% of extra-adrenal pheochromocytomas.[2,8] The tumor in our case was found in the vicinity of the inferior mesenteric artery.

Glenn and Gray[3] reported four patients with functioning tumors of the organ of the Zuckerkandl and reviewed other cases in the literature. These tumors secrete catecholamines and the symptoms are attributable to excessive circulating catecholamines. Measurements of urinary metanephrine remains the principal biochemical diagnostic test, having an accuracy rate of 95%. In our case 24-hour urinary metanephrine and catecholamine levels were elevated before surgery and the values returned to within normal range after surgery. This test is particularly recommended in certain suspect groups of patients who are at higher risk of developing pheochromocytomas.[8] Provocative tests are of limited value.[5] Recently, tomography and selective angiography have improved the ability to localize the tumor.[2] The classic location of the tumor of the organ of Zuckerkandl is in the retroperitoneal tissue lateral to or overlying the lower portion of the abdominal aorta in the vicinity of the inferior mesenteric artery. These tumors are partially or totally encapsulated and have an ovoid or lobulated light tan-gray to reddish appearance. Our case was at the typical location and had all the gross and microscopic patterns of classic para-aortic paraganglioma. The histologic pattern of para-aortic paraganglioma consists of a stroma rich in blood vessels and sinusoids, surrounding nests of polygonal cells with finely granular and homogeneous eosinophilic cytoplasm. The cells have conspicuous round-to-oval nuclei. A few multinucleated giant cells and mitotic bodies are seen.[1] Paragangliomas must be differentiated from carcinoid, hemangiopericytoma, alveolar soft tissue sarcoma, and metastatic carcinoma.[1,3] The use of special stains and histochemical and cytochemical characteristics is summarized by Glenner and Grimley.[1] Histologic appearance is not consistently related to catecholamine secretion. Histologic appearance cannot reliably distinguish between malignant and benign tumors; the only reliable criterion for the diagnosis of malignancy is demonstration of invasion of adjacent organs or of metastasis. Extra-adrenal pheochromocytomas tend to be five to ten times more malignant than adrenal pheochromocytomas.[2,8] Extra-adrenal pheochromocytomas may be frequently associated with multiple endocrine neoplasia types I, IIA, and IIB. The treatment of choice is excision of the primary tumor and follow-up. Solitary and limited metastatic lesions are treated by surgical resection.[9] Karasov et al[7] recently described a patient who had 21 paraganglions removed between age 13 and 17.

Acknowledgments. The authors thank the staff of the Pathology Department and Suzanne Rowe for assistance in preparing the manuscript.

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Carotid body tumor as reversible cause of recurrent syncope

LEON ROSENKRANZ, MD, A. ROBERT SCHELL, MD

Carotid body tumors usually appear as expanding neck masses. Although commonly asymptomatic, they may produce local pain, headaches, and dizziness.[1-3] Since they grow in proximity to the carotid artery, the carotid sinus, and the vagus nerve, these tumors might be expected to cause syncopal episodes; however, this symptom has rarely been reported in the literature. We present a case of a carotid body tumor which produced orthostatic hypotension, relative bradycardia, and syncope in a patient whose symptoms cleared after resection of the tumor.

CASE REPORT

A 60-year-old man with a large, left-sided neck mass was admitted to Coney Island Hospital in February 1982 after a syncopal episode. The mass had been present since 1963. In 1969 an arteriogram disclosed bilateral carotid body tumors, much larger on the left side. Surgical excision was attempted unsuccessfully, and the patient received a course of radiotherapy. He returned to the clinic regularly for many years. His sole complaint was chronic vertigo when rising from a seated to a standing position. In the year prior to admission, the patient developed the syncopal episodes which prompted his entry into the hospital.

Physical examination showed a nonpulsatile 5 × 5-cm mass on the left side of the neck. Blood pressure lying down was 150/84 mm Hg; standing up, the pressure was 86/60 mm Hg. There was no simultaneous increase in pulse rate. The patient was neither volume-depleted nor anemic. The remainder of the physical examination as well as the neurologic examination was normal. A complete workup, including computerized tomography of the brain and ambulatory cardiac monitoring, showed no abnormalities. An angiogram demonstrated bilateral tumors (Figure), and the patient underwent resection of the left-sided tumor with graft replacement of the adjacent segment of carotid artery.

Five months postoperatively, the patient reported no episodes of syncope and only a single episode of vertigo since his surgery. On reexamination, blood pressure now dropped from 160/90 mm Hg to 120/86 mm Hg when the patient stood up, and his pulse rate increased from 64 to 76 beats per minute. The patient continues to be free of symptoms 12 months after surgery.

DISCUSSION

This patient with bilateral carotid body tumors and chronic syncope underwent surgical resection of the larger tumor with subsidence of symptoms. Following surgery, he had less dramatic orthostatic changes of his blood pressure and he was able to mount a compensatory tachycardia.

Syncope has rarely been mentioned as a symptom of carotid body tumors. In 1947, McSwain and Spencer[4] described two patients in whom syncope preceded the appearance of palpable neck masses. Both patients subsequently developed carotid body tumors. In 1967, Farr[5] reported a series of 37 patients with carotid body tumors; one had syncope and six had carotid sinus "sensitivity" on compression of the neck mass. In 1977, Farr[6] again reported two patients with carotid body tumors whose pulse rates slowed with compression of the tumor. Other neck tumors may produce syncope, such

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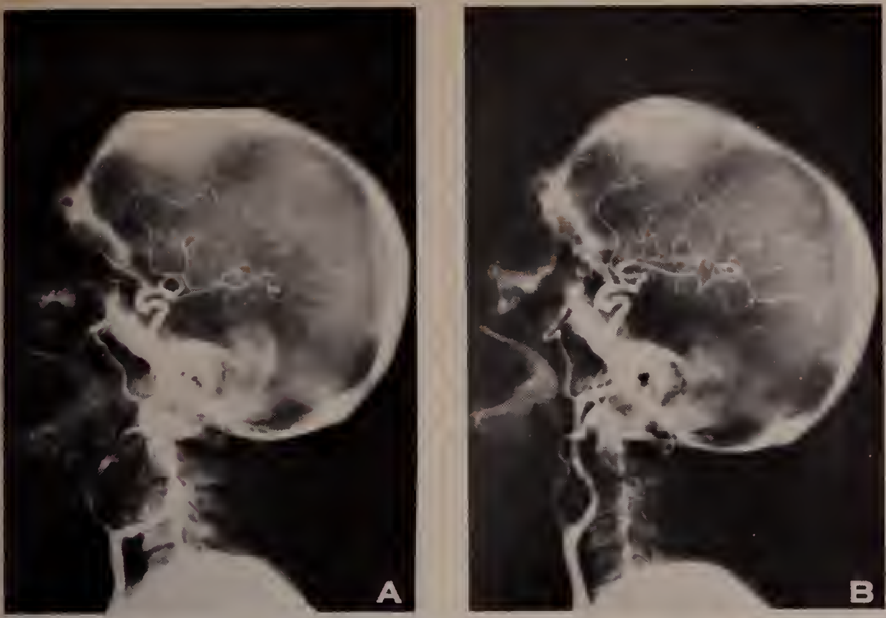
From the Departments of Medicine (Dr Rosenkranz) and Neurology (Dr Schell), Coney Island Hospital, Brooklyn.

Address correspondence to Dr Rosenkranz, 395 South End Ave, Apt 12L, New York, NY 10280.



Carotid arteriogram showing tumors involving the left (A) and right (B) carotid bodies and displacing the carotid arteries.

as the cases described by Bardin et al[7] in which the symptoms were produced by squamous cell carcinomas growing near the carotid bifurcation.

The carotid body functions physiologically to adjust respiratory rate and drive in response to metabolic needs. Disruption of the carotid body by tumor should not alter level of consciousness. However, the carotid sinus, an adjacent structure, acts to maintain blood pressure and pulse in response to postural changes. Compression of the carotid sinus by a mass might well lead to both severe orthostatic hypotension and failure of the heart rate to increase, with resultant syncope.[8] Similarly, compression of the carotid artery or of the vagus nerve by a carotid body tumor could also cause neurologic deficits.

We believe that there are two lessons to be learned from our case. First, that syncope may be a proper indication for surgery on a carotid body tumor, even though the tumor may otherwise be causing few symptoms. Second, the presence of spontaneous syncope with no other apparent cause should prompt the physician to search for a neck mass, particularly if the patient shows symptoms of blunted sympathetic reflexes, such as orthostatic hypotension and relative bradycardia. If no mass is palpable, ultrasound examination of the neck, followed by arteriography, when indicated, may disclose a carotid body tumor.[9,10] If found, this tumor can be resected; the patient's symptoms may cease.

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Glomus tumor of the stomach

ELSA VALDERRAMA, MD, EDDY LILAVOIS, MD, LEROY R. LEVIN, MD,
LEONARD B. KAHN, MMED

Glomus tumor has been described as an enlarged caricature of the glomus apparatus.[1] The glomus apparatus was first described by William Wood in 1812,[2] and was considered to be present only in the skin at the dermoepidermal junction of the subungual region. Later its occurrence was demonstrated in other parts of the skin[3,4] and also in viscera, including the stomach.[5,6] The glomus tumor of the stomach is an uncommon neoplasm which usually behaves in a benign fashion. Gastrointestinal bleeding, peptic ulcer-like symptoms, and the presence of an antral mass on barium studies are the usual clinical features. There are no specific features that distinguish this tumor from the more frequently occurring gastric carcinoma. It is important for the pathologist to be able to recognize it at the time of a frozen section in order to avoid extensive surgery.

CASE REPORT

A 54-year-old woman was admitted to the hospital after having passed black stool for four weeks associated with changes in bowel

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From the Departments of Laboratories (Drs Valderrama, Lilavois, and Dr Kahn, Chairman) and Surgery (Dr Levin), Long Island Jewish-Hillside Medical Center, New Hyde Park, New York

Address correspondence to Dr Valderrama, Staff Pathologist, Department of Laboratories, Long Island Jewish-Hillside Medical Center, 270-05 76th Ave, New Hyde Park, NY 11042.

habits. An upper gastrointestinal (GI) series performed ten years previously was reported as normal. Physical examination revealed an obese woman in moderate distress with a blood pressure of 135/75 and a pulse rate of 80/min. The remainder of the physical examination and the laboratory tests were within normal limits. Gastroscopy and an upper GI-series demonstrated a submucosal mass near the pylorus (Fig 1). The patient was treated with cimetidine (Tagamet) for one week, and a repeat upper GI series showed no change in the gastric mass. A partial gastrectomy was performed and the patient is alive and well without evidence of recurrent disease 20 months after operation.

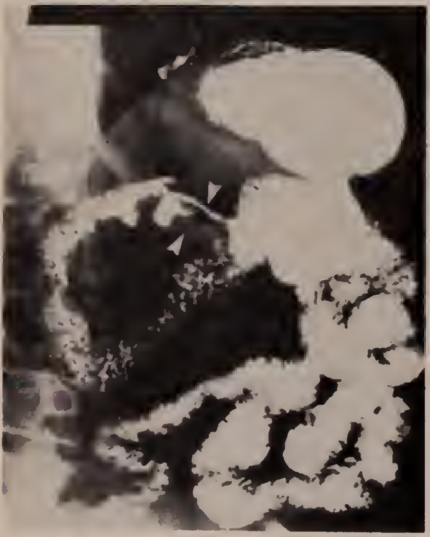

FIGURE 1. Upper gastrointestinal series showing submucosal mass near pylorus (arrows).

PATHOLOGIC FINDINGS

Macroscopic features. The resected specimen consisted of a segment of stomach including the pylorus and a ring of duodenum measuring 13 cm along the greater curvature, 8 cm along the lesser curvature, and 8 cm in diameter at the proximal line of resection. A tumor mass measuring 3 × 2.5 cm was present in the posterior wall 1 cm proximal to the pylorus. The tumor formed a protruding mass on both the serosal and mucosal surfaces. The mucosa covering the tumor was intact. On section, the tumor was well circumscribed, had a rounded shape, and was located entirely within the muscularis propia (Fig 2).

Microscopic features. The tumor was surrounded by a pseudocapsule formed by compressed and partially hyalinized smooth muscle while bands of smooth muscle extended into and partially subdivided the tumor. The tumor cells were small, uniform, and polygonal with eosinophilic or clear cytoplasm. The nucleus was regular and round and contained reticulated chromatin. Neither mitoses nor cellular pleomorphism was noted. In some areas, the tumor cells were arranged in solid sheets with scanty stroma containing compressed capillaries. In other areas, the tumor was characterized by the presence of numerous dilated and tortuous endothelial-lined vascular channels surrounded by nests or larger lobules of tumor cells.

The endothelial cells were separated from the tumor cells by a thin layer of fibrocollagenous tissue. Lobules of tumor cells also invaginated the vascular lumina producing a pseudopapillary pattern. Nests of tumor cells were also isolated within the muscle wall away from the main tumor mass. Some of these nests formed structures reminiscent of the normal glomus body, having an afferent small arteriole and efferent venule separated by a tortuous vessel surrounded by tumor cells (Sucquet-Hoyer anastomosis) (Fig 3). A reticulin stain showed abundant reticulin fibers surrounding individual cells or groups of two to three cells. No nerve fibers were identified in either the hematoxylin and eosin stain or the Bodian stain.

Electron microscopic features. Formalin fixed tissue was processed for electron microscopic studies. Although advanced autolytic changes were present, some of the characteristics of the glomus cells were recognizable. The polygonal tumor cells had straight plasma membranes surrounded by an electron dense basement membrane-like material. A few pinocytic vesicles were seen. Most of the organelles were destroyed, but in some cells rough and smooth endoplasmic reticulum and microfilaments with condensation zones could be recognized.

DISCUSSION

The glomus tumor is derived from a specialized structure, the glomus apparatus or "neuromyoarterial glomus," which is present wherever arteriovenous anastomoses exist.[1-4] The glomus apparatus consists of three vascular components, an afferent artery separated from an efferent venule by branched and convoluted channels, the so-called Sucquet-Hoyer anastomosis. The convoluted channels have narrow lumina and a single layer of endothelium encased by multiple layers of epithelioid glomus cells.[7] A sheet of loose connective tissue with many nerve fibers surrounds the area of anastomosis. The principal function of this structure appears to be local readjustment of the vascular flow mediated by factors present within the vascular lumen.[7-10] The glomus apparatus was described initially by William Wood (1812)[2] in the skin at the dermoepidermal junction of the subungual region, but later it was found also in other acral areas of the skin[1,3,4] and in some viscera including the choroid of the eye, trachea, mediastinum, kidney, uterus, vagina, bone, joints, skeletal muscle, soft tissue, and stomach.[5,6] In the stomach, it has been found in the mucosa, submucosa, and serosa, most frequently on the greater curvature.[6]

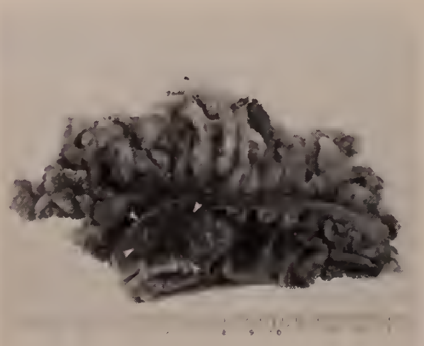

FIGURE 2. Longitudinal sections of stomach. Intramural tumor protruding into lumen and covered by intact mucosa seen close to pylorus (arrows).

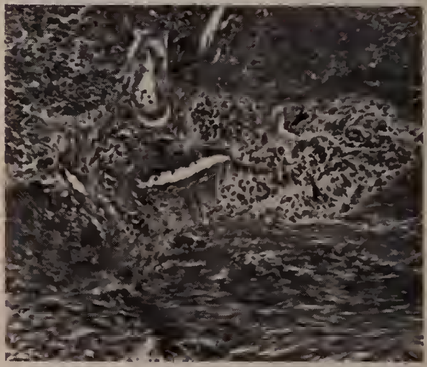

FIGURE 3. Nests of tumor cells found isolated within muscle coat. Note structure reminiscent of normal glomus body composed of afferent artery (single arrow), efferent vein (double arrow), and tortuous vessel (arrow head) surrounded by tumor cells (Sucquet-Hoyer anastomosis). Hematoxylin and eosin, original magnification × 225.

Gastric glomus tumor is an unusual neoplasm. To date, more than 70 cases have been reported.[1,8-19] An analysis of 72 cases (Tables I and II) indicates a predominant location within the muscularis propria with extension to the serosa or submucosa. The lesion may protrude into the lumen forming a polypoid mass. The mucosa covering the tumor was described as intact in two thirds of the cases. An ulcer was identified in only 19 cases and this finding correlates with the number of patients who presented with gastrointestinal bleeding (24 patients). The size of the tumor ranged from 0.7 to 25 cm in largest diameter but the majority were less

TABLE I. Clinical Features of Glomus Tumor of Stomach—72 Cases

Age	Range	18–89 years
	Mean	58.5 years
Sex	Male	37 cases
	Female	35 cases
Symptoms	Ulcer	29 cases
	Bleeding	24 cases
	Incidental	19 cases

TABLE II. Pathologic Features of Glomus Tumor of the Stomach—72 Cases

Size	0.7–25 cm in largest diameter	
Location	Greater curvature	39 cases
	Lesser curvature	14 cases
	Anterior wall	8 cases
	Posterior wall	5 cases
	Antral or pyloric	3 cases
	No mention	3 cases
Ulceration		19 cases
Infiltration or metastasis		3 cases

than 4 cm in diameter. Nearly all of the tumors behaved in a benign fashion even though some grew large and infiltrated surrounding tissue.[16–18] One of the cases reported in the Russian literature developed metastases to lymph nodes and liver, but the patient survived for 15 years.[16] There are no specific clinical features that point to a diagnosis of gastric glomus tumor. The pathologist needs to be aware of the existence of this lesion in order to differentiate it from more common gastric neoplasms, especially malignant growths, when he is called to make a diagnosis by frozen section. The recognition of this tumor could avoid radical surgical resection.

The glomus tumor must be differentiated from a carcinoid, hemangiopericytoma, leiomyoblastoma, undifferentiated small cell carcinoma, and lymphoma.[8,9,13,15] The organoid and angiomatous pattern and the regularity and uniformity of the polygonal cells are characteristic features of the glomus tumor. A carcinoid tumor lacks the vascular component and contains argyrophilic granules. Hemangiopericytoma also has a rich vascular network producing a "staghorn" pattern of dilated vascular channels, but the tumor cells are spindle shaped rather than polygonal. Leiomyoblastoma also has spindle shaped sarcoplasmic-rich cells in addition to polygonal cells with clear cytoplasm and usually shows considerable nuclear atypia. By electron microscopy the glomus cells have characteristics similar to those of smooth muscle cells, namely, regular cytoplasmic membranes surrounded by a basement membrane-like material, pinocytic vesicles, and cytoplasmic microfilaments with foci of condensation. The glomus cell is considered to be a modified smooth muscle cell with specialized function.[10,13,15,19] Differentiation of glomus tumor from hemangiopericytoma and from small round cell leiomyoblastoma by electron microscopy may be difficult because of the similar histogenesis and organelle content of these cell types.

Acknowledgments. The authors wish to thank Malka Tenenbaum, Nathan Kantor, and William Oxberry for their technical and photographic assistance, as well as Joan M. Sullivan, for her assistance in preparing the manuscript.

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Hypocalcemia in metastatic bone disease: metabolic and radionuclide studies of a case

GARY M. PEPPER, MD, ARNOLD M. STRASHUN, MD, STANLEY J. GOLDSMITH, MD

Hypocalcemia in association with metastatic bone disease is considered to be a rare clinical occurrence. However, in 1973, a retrospective study of patients with bony metastases of various origins demonstrated mild hypocalcemia in 16% of this group.[1]

Studies utilizing ^{45}Ca have shown that patients with blastic metastases have an abnormal avidity for the tracer.[2,3] The

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From the Department of Medicine, Brookdale Hospital Medical Center, Brooklyn, NY and the Departments of Medicine and Radiology, Mount Sinai Hospital and Medical Center, New York City

Address correspondence to Department of Medicine, The Brookdale Hospital Medical Center, Brooklyn, NY 11212 (Dr Pepper).

cause of this increased avidity has not been clarified. Likewise, it is not clear why hypocalcemia occurs in certain patients with blastic metastases and not in others.

We recently had the opportunity to study a patient with blastic metastases and profound hypocalcemia. Several factors which individually or together could lead to such hypocalcemia were demonstrated.

CASE REPORT

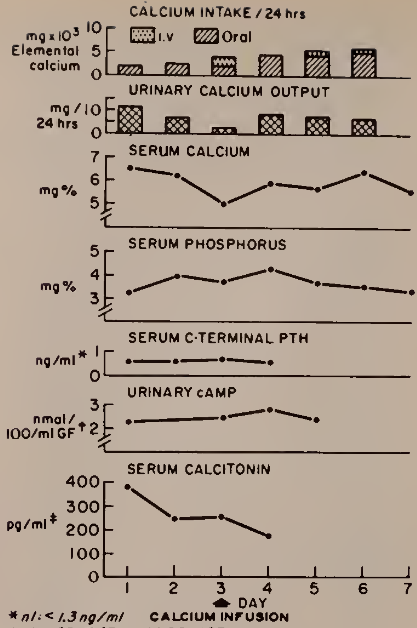
A 79-year-old woman was admitted in February 1980 to Mount Sinai Hospital and Medical Center for evaluation of hypocalcemia. Three years before admission, breast carcinoma was first diagnosed and treated with radical mastectomy and radiotherapy. Six months later, blastic and lytic bone metastases were documented by x-ray and treatment with various chemotherapeutic regimens was undertaken, including cyclophosphamide (Cytoxan), 5-fluorouracil, methotrexate, fluoxymesterone tablets (Halotestin), and doxorubicin hydrochloride (Adriamycin).

Forty years prior to admission, the patient had undergone partial thyroidectomy for an overactive thyroid. Up until two months prior to admission, she had been eumetabolic and eucalcemic, being maintained on 1 grain of dessicated thyroid daily.

Five months prior to admission, serum calcium level was 9.0 mg/dL. In February 1980, the patient complained of increasing fatigue and repeat screening revealed a calcium level of 6.3 mg/dL. Skeletal survey and ^{99m}Tc pyrophosphate bone scanning showed progression of her disease, with diffuse osteolytic and osteoblastic metastases.

At admission two weeks later, the calcium level had fallen to 4.7 mg/dL (normal 8.5 to 11 mg/dL), while the phosphate level was 5.3 mg/dL (normal 3.5 to 4.7 mg/dL); albumin 3.2 g/dL (normal 3.5 to 4.9 g/dL); total protein, 5.6 g/dL (normal 6.0 to 8.3 g/dL); alkaline phosphatase 633 mU/dL (normal 30 to 90 mU/dL); total bilirubin, 1.3 mg/dL (normal 1.0 to 1.2 mg/dL); SGOT, 80 mU/mL (normal 1 to 53 mU/mL); thyroxine (T_4), 5.3 μg/dL (normal 4.0 to 11.5 μg/dL); T_3 resin uptake, 25% (normal 25% to 35%); thyroid stimulating hormone (TSH), 3.5 μIU/mL (normal <8.8 μIU/mL). Values for magnesium, electrolytes, cholesterol, BUN, creatinine, and prothrombin time were all within normal limits. Physical examination was remarkable for a mastectomy scar and a positive Trousseau's and Chvostek's sign. The EKG revealed a prolonged QT interval of 0.43 sec at 92 beats/min. Subsequently, the patient had a ^{99m}Tc sulfur colloid liver-spleen scan which demonstrated metastatic disease within the liver.

Replacement therapy with intravenous and oral calcium plus vitamin D was initiated. Levothyroxine Sodium (Synthroid) 0.15 mg daily replaced dessicated thyroid therapy. The equivalent of greater than 7,000 mg of elemental calcium (6,000 mg intravenously and 1,600 mg orally) plus 50,000 IU of vitamin D was required daily to increase the serum calcium level above 7 mg/dL. The refractory nature of the hypocalcemia over a one-month period prompted further study.



** nl: < 1.3 ng/ml*

† nl: 1.83 - 4.47 nmol/100ml GF

‡ nl: < 150 pg/ml

N-terminal PTH was undetectable throughout the study

FIGURE 1. Balance study data demonstrating intravenous (IV) and oral intake of calcium *v* urinary excretion of calcium. Also shown are serum levels of calcium, phosphorus, carboxy-terminal PTH (amino-terminal was undetectable throughout), calcitonin, and urinary excretion of cAMP.

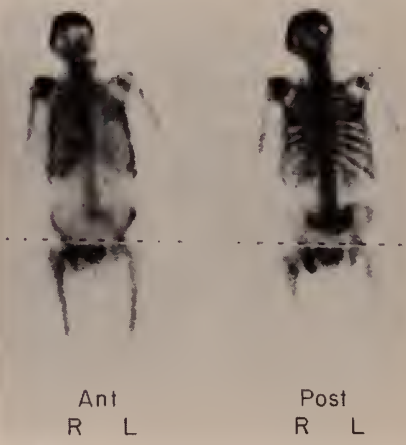


FIGURE 2. Whole body bone scan obtained two hours after IV administration of 20mCi ^{99m}Tc pyrophosphate. Scan reveals focal but widespread metastases demonstrated by increases in radiotracer uptake involving skull, entire vertebral column, ribs, clavicle, pelvis, both humeri and femurs. Reduced renal activity and a large area of decreased activity in left side of chest represent effect of radiation therapy.

During the last two weeks of life, congestive heart failure developed. The patient subsequently died of cardiopulmonary arrest. Postmortem examination was refused.

MATERIALS AND METHODS

The patient was maintained on a 1,000-mg calcium diet. Additional calcium supplementation was given parenterally and orally as calcium gluconate and carbonate. Vitamin D was given orally as vitamin D_2.

In order to assess the patient's avidity for a bone-seeking tracer, a 24-hr study of ^{99m}Tc pyrophosphate retention was performed. A bolus of 20 mCi of ^{99m}Tc pyrophosphate was injected intravenously and for the next 24 hr urine was collected and then assayed for radioactive content. ^{99m}Tc pyrophosphate is believed to undergo chemadsorption at the surface of bone mineral in a manner similar to calcium deposition.[4] By determining the differential uptake of this tracer in the skeleton versus competing renal clearance, quantitation of bone formation was achieved.

The patient underwent an intensive six-day study of various hormonal and metabolic parameters. The dosage of calcium was adjusted in an attempt to produce a stable serum calcium level (Fig 1). Up to 2,000 mg parenterally of elemental calcium as calcium gluconate and up to 4,000 mg orally of elemental calcium as calcium carbonate and gluconate were administerd daily. Blood samples on the days of the study as noted in Figure 1 were assayed for calcium, phosphorus, magnesium, and creatinine. Additionally, immunoreactive calcitonin,[5] amino-terminal parathyroid hormone (PTH), and carboxy-terminal PTH[6] were measured by B. Roos, MD. 25(OH) vitamin D[7] and $1,25(OH)_2$ vitamin D[8] were measured by competitive protein binding assays by Hoffman LaRoche laboratories. Twenty-four hour urine collections were assayed for volume, creatinine, calcium, phosphorus, and magnesium. Urinary cAMP was measured by A. Broadus, MD by immunoassay.[9] The renal tubular maxmum for phosphate reabsorption per liter of glomerular filtrate ($TmPO_4$/GFR) was measured on three samples from different days by a modification of the method of Walton and Bijvoet. All stool was collected during the six-day period.

On day 3 of the study, the equivalent of 2,000 mg of elemental calcium was infused intravenously over 4 hr; serum calcium, PTH, calcitonin, and urinary cAMP were measured before and after the calcium infusion.

RESULTS

Bone scintiscan revealed a pattern consistent with multiple skeletal metastases without evidence of unusual extraskeletal uptake (Fig 2). The 24-hr ^{99m}Tc pyrophosphate retention was elevated at 80% (normal 40% to 45%).[11] Creatinine clearance at this time was 90 mL/min. These findings are consistent with increased bone avidity for calcium. Similar findings have been reported in association with other clinical states in which calcium uptake by bone is heightened.[4,12] This study is, to our knowledge, the first of its kind to be reported in this setting. Urinary calcium excretion was extremely low throughout the course, despite substantial intravenous and oral replacement. Both the amino-terminal and carboxy-terminal PTH and UcAMP reflected a hypoparathyroid state when considered in association with the serum calcium level. Consistent with this was the $TmPO_4$/GFR value of 4.8 ± 0.06 mg/dL (normal 2.5 ± 4.2 mg/dL), reflecting a high degree of renal phosphate conservation. Serum calcitonin was elevated despite the severe hypocalcemia. Serum magnesium remained in the normal range throughout the study.

25(OH) vitamin D was normal at 29 ng/mL and 24 ng/mL on two different days during the study period, while $1,25(OH)_2$ vitamin D levels were reduced at 4 pg/mL and 10 pg/mL, respectively (normal 25(OH) vitamin D: 10 to 50 ng/mL; $1,25(OH)_2$ vitamin D: 20 to 45 pg/mL).

The quantity of stool produced during these six days was less than 400 g and reflected the patient's poor oral intake. Clinically significant malabsorption with this volume of stool is thought unlikely. However, a quantitation of stool calcium was not done. Normal clotting parameters, cholesterol level, and serum magnesium levels in this patient support the likelihood of normal or near normal gastrointestinal function although it does not rule out isolated calcium malabsorption. During the calcium infusion study, the serum calcium level rose by 1.3 mg/dL. Serum calcitonin declined from 256 to 168 pg/mL, whereas UcAMP and amino-terminal and carboxy-terminal PTH remained virtually unchanged.

DISCUSSION

Relative hypoparathyroid was documented in this case by the finding of low levels of amino-terminal and carboxy-terminal PTH and of urinary cAMP in the presence of hypocalcemia. The profound and refractory nature of the hypocalcemia in this case can be only partially explained by the lack of an adequate parathyroid hormone response however, as the hypocalcemia of hypoparathyroidism is usually much more amenable to therapy.[13] The onset of hypoparathyroidism 40 years after thyroidectomy suggests the existence of decreased functional parathyroid reserve which was then subjected to conditions of enhanced calcium need.[6] The phenomenon of decreased parathyroid reserve has been documented to occur frequently after the form of neck surgery this patient underwent.[14] Spontaneous relative hypoparathyroidism has been reported in several other cases of hypocalcemia associated with metastatic disease, and was felt to be an important contributor to the pathogenesis of the hypocalcemia.[13,15,16]

$1,25(OH)_2$ vitamin D levels were low with normal 25(OH) vitamin D levels while the patient was on vitamin D supplementation. $1,25(OH)_2$ vitamin D levels are reduced in hypoparathyroidism, as PTH is essential for the 1-hydroxylation of the precursor molecule, 25(OH) vitamin D.[17] Tumor-related factors may also contribute to the low $1,25(OH)_2$ vitamin D levels, as low $1,25(OH)_2$ vitamin D with normal 25(OH) vitamin D levels have been noted in association with malignant conditions without hypoparathyroidism.[18,19] The cause of this may be through inhibition of 1-hydroxylation of 25(OH) vitamin D by a tumor-produced factor. In two recent reports of hypocalcemia occurring in association with blastic metastases, 25(OH) vitamin D levels were reported to be both normal[20] and low.[15] $1,25(OH)_2$ vitamin D levels were low in the one patient in whom it was measured.[15] In a state of $1,25(OH)_2$ vitamin D deficiency, hypocalcemia would be promoted by the decreased gut resorption of calcium.[17] Decreased absorption of calcium from the gut could therefore have participated in the genesis of this patient's severe form of hypocalcemia.

The elevation of serum calcitonin level may also have relevance to the maintenance of hypocalcemia. A substantial portion of tumors of various origins have been shown to be associated with elevated serum calcitonin levels.[21] This is believed to be the result of the ectopic production of this hormone by the tumor itself. The failure of calcitonin to increase after the calcium infusion would rule out a concurrent medullary carcinoma of the thyroid as the source of calcitonin in the present case.[22]

In the presence of low PTH and $1,25(OH)_2$ vitamin D levels, calcitonin can exert a persistent hypocalcemia effect via inhibition of bone resorption.[23,24] Although its role in promoting hypocalcemia in this case is unproved, calcitonin levels were also elevated in a strikingly similar case of refractory hypocalcemia in association with metastatic bone disease and reduced PTH and $1,25(OH)_2$ vitamin D levels.[15]

An elevated retention of ^{99m}Tc pyrophosphate without evidence of unusual extraskeletal uptake was demonstrated in the presence of a low PTH level. An additional impetus for enhanced skeletal avidity for calcium therefore existed. As calcitonin exerts its major hypocalcemic effect by inhibiting bone resorption rather than by stimulating new bone formation,[25] none of the hormonal abnormalities so far outlined would account for any degree of increased calcium uptake. It is speculated that a process either local to the sites of blastic activity or mediated generally by a tumor-related substance is most likely to be responsible. In either case, the bone acted as a virtually inexhaustible calcium sink capable of absorbing substantial amounts of calcium daily. This, in concert with a permissive hormonal milieu, generated a uniquely severe and refractory form of hypocalcemia.

SUMMARY

A patient with refractory hypocalcemia, associated with metastatic bone disease, was studied. Greater than 7,000 mg of elemental calcium plus 50,000 IU of vitamin D daily, were required to raise serum calcium levels. Amino-terminal and carboxy-terminal parathyroid hormone and urinary cyclic AMP levels were inappropriately low, while calcitonin levels were unexpectedly elevated. Reduced $1,25(OH)_2$ vitamin D with normal 25 (OH) vitamin D levels were found. A 24-hour study of ^{99m}Tc pyrophosphate retention provided evidence of enhanced skeletal avidity for calcium in this setting. We conclude that hormonal or local tumor-related factors created a profound calcium demand in a setting of impaired homeostatic mechnisms. An unusually severe and resistant form of hypocalcemia resulted.

Acknowledgments. We wish to express our appreciation to Dorothy T. Krieger, MD and Theodore W. AvRuskin, MD for their valuable comments on this manuscript.

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Politics and the NIH:

Committee studies reorganization

"... a new institute could be created for every known disease."

Should the National Institutes of Health (NIH) be broken up into individual institutions, each one devoted to a single disease or organ system? And to what degree would such separate institutes be subject to pressure from voluntary health agencies, politicians, and others who want a say in what type of research "their" institute should be doing?

At the request of the NIH, the Institute of Medicine has appointed a committee to review the organization and goals of the NIH. The Institute of Medicine is part of the National Academy of Sciences, a nongovernmental organization of scientists and engineers that serves in an advisory capacity to the government in matters of science and engineering.

The Committee for the Study of the Organizational Structure of the National Institutes of Health is chaired by James D. Ebert, PHD, President of the Carnegie Institution of Washington, DC. It is charged with analyzing the evolution of the NIH and NIH's handling of problems requiring interdisciplinary research. The Ebert committee will recommend guidelines for making the NIH more responsive to changing research goals of scientists and demands by the public for investigations in specific areas.

CONGRESS MAKES A MOVE

One option, the creation of more institutes to address specific diseases, has been criticized by some scientists. But supporters seem to be more successful than detractors. A bill (HR 2350) passed by Congress in November 1983 establishes a new National Institute of Arthritis and Musculoskeletal Diseases, an idea promoted by the Arthritis Foundation. The bill, sponsored by Henry A. Waxman (D-CA), also creates among other things a new National Commission on Orphan Diseases, a 15-member presidential commission on the human applications of genetic engineering and programs that will fund specific diseases, such as Alzheimer's disease, sudden infant death syndrome, and neurofibromatosis.

HR 2350 also contains a provision for a study of the organization and management of the NIH. It was this provision that prompted formation of the Ebert committee even before the bill was passed. The committee is addressing three broad issues related to the NIH. Each issue is being studied by a separate panel of scientists and health care professionals that will inform the committee of its findings.

The first panel (Historical Issues) will examine the evolution of the mission and structure of the NIH, including how and why new institutes were added in the past, and the NIH's relationships to its parent agency, the Department of Health and Human Services, and to Congress. The second panel (Current Structure) will study the organization and administration of NIH, allocation of research funds by NIH, and the function of agencies that have been proposed as additions to the NIH.

The third panel (Alternatives) will focus on new ways of setting research priorities and funding research grant proposals.

NIH CALLS PUBLIC HEARING

As part of an effort to guide committee and panel deliberations, public hearings were held last September 26 and 27 at the National Academy of Sciences in Washington, DC.

The meeting was publicized by means of mailings to professional and voluntary health groups and by announcements in *Science* (targeted to biomedical researchers) and the *New England Journal of Medicine* (targeted to practicing physicians) published shortly before the meeting. Fifteen speakers were selected by Michael A. Stoto, PHD, director of the study, from a pool of about 45 applicants. Dr Stoto told the *Journal* that he chose speakers whom he believed represented a broad spectrum of opinions on the matter. But he said that the choices were based on what they had to say rather than which organizations they were representing.

Some of the views reflected the political pressure that initiated formation of the committee in the first place. This was especially evident in the testimony of those speakers advocating major changes in the NIH that would make it more responsive to their own voluntary health agency (such as the Arthritis Foundation) or professional organizations (such as the Association of Academic Departments of Otolaryngology).

The majority of speakers were not in

NYJ NewsFeatures is compiled and written by Marc Kusinitz, PHD.

Scientists must be "opportunistic" and learn to take advantage of the system.

favor of establishing new institutes, but their views on what changes were needed at NIH were almost as varied as the organizations represented at the hearing.

FOR NEW INSTITUTES

William McHugh, DDS, president of the American Association for Dental Research, said that although the structure of the NIH was sound, there was a danger "that a new institute could be created for every known disease." But a joint statement from the American Association for Dental Research, the American Association of Dental Schools, and the American Dental Association criticized the NIH for its tendency to ignore dentistry when allocating research funds. In seeming contrast to Dr McHugh's warning, the statement said that the NIH should develop guidelines, with the help of the Ebert committee, for establishing new institutes.

William F. Bridgers, MD, dean of the School of Public Health at the University of Alabama and president of the Association of Schools of Public Health, proposed a new Institute of Public Health as a means to ensure funding for research in preventive medicine.

Dr Bridgers warned that "by focusing only on cure, in most cases a disease is dealt with after the fact."

"He does research in order to get grants, when he should be getting grants in order to do research."

Perhaps the strongest case for establishing a new institute at the NIH was made by Bobby R. Alford, MD, professor and chairman of the Department of Otorhinolaryngology and Communicative Sciences at Baylor College of Medicine. Speaking on behalf of the Association of Departments of Otolaryngology, Dr Alford proposed the establishment of a National Ear, Nose and Throat Institute. According to Dr Alford, there is inadequate research in otolaryngologic areas at the National Institutes of Neurological and Communicative Disorders and Stroke. In contrast, Dr Alford pointed out that ophthalmologic research has benefited from the establishment of a National Eye Institute.

In support of establishing new institutes, Frederick C. McDuffie, MD, senior vice president of the Medical Group of the Arthritis Foundation said that scientists must be "opportunistic" and learn how to take advantage of the system.

INTERDISCIPLINARY RESEARCH?

The American Medical Association, although not represented by a speaker, submitted a written opinion that opposed addition of new disease-specific institutes within NIH. The AMA stated that such institutes could lead to greater and undesirable fragmentation of research efforts and reduce full consideration of biologic interrelationships. The AMA statement, in contrast to Dr Alford's view, also said that new institutes would increase overhead and administrative costs and thus reduce funds available for research.

Samuel H. Preston, PHD, a professor at the Population Study Center, University of Pennsylvania and president-elect of the Population Association of America, also spoke in favor of interdisciplinary research and the enhanced integration of the behavioral and social sciences at NIH.

Citing the interdisciplinary approach required by physicians treating lung disease, Gareth M. Green, MD, editor of the American Lung Association journal, *American Review of Respiratory Disease*, suggested that the need for new institutes could be eliminated by establishing disease-oriented, interagency committees, which would recommend expenditures for each institute of the NIH.

"There is wisdom," Dr Green said, "in developing specific administrative mechanisms to address applied needs in medical care, disease prevention, and public health through the institutes' programs while shielding basic research functions from distortions resulting from the political process."

One way to accomplish this, according to Melvin H. van Woert, MD, medical director of the National Organization of Rare Disorders (NORD), and professor of neurology and pharmacology at Mount Sinai School of Medicine in New York, is through greater integration of all institutes under a stronger central administration than exists today.

Dr Van Woert, speaking on behalf of NORD, criticized the "disease-of-the-month" phenomenon in which pressure groups try to increase NIH funding for research in their area of interest.

RESLICING THE NIH PIE

But whatever the benefits of interdisciplinary studies, they may not always improve the health of certain segments of society. This potential problem was illustrated, however inadvertently, by two speakers, one representing the American Heart Association (AHA), which is against setting up new institutes, and the other representing the Association of Minority Health Professions Schools (AMHPS).

Mary Jane Jesse, MD, president of the AHA, praised the interdisciplinary organization of the National Heart Lung and Blood Institute, which she credited with contributing in large part to declining mortality rates due to cardiovascular diseases. But the work of that institute may benefit whites more than minorities. While not referring to any specific institute at NIH, David Satcher, MD, PHD, speaking as president of AMHPS, quoted a 1982-1983 study conducted by that organization that showed that hypertension and strokes kill more blacks than whites.

Dr Satcher said that "Just as the National Institutes of Health found it necessary many times in the past to focus on special problems within the institutes, whether by setting up an entire institute or by developing new programs, it is our feeling that it is now time to focus on the special problem of continuing relative deficiencies in the health status and health care availability to blacks and other minorities in this country."

Dr Satcher called for increased funding of black health professions schools to bolster their research infrastructure so these institutions can "compete for the resources of the NIH and become a channel through which the NIH can focus on solving the health problems of minority communities."

RETHINKING PEER REVIEW

Although the politics of establishing new institutes was the major issue on the minds of most speakers, some also took the opportunity to suggest changes in the peer review system by which study sections in various disciplines at the NIH recommend or reject outside research grant proposals.

J. Palmer Saunders, PHD, professor of pharmacology and toxicology and dean of the University of Texas Graduate School of Biomedical Sciences at Galveston, argued that the current peer review system often—if not always—reflects the prejudices, fashions, and biases of its members. He cited the example of the concept of viral etiology for cancer, which traditional virologists in the late 1950s did not accept.

Dr Saunders suggested that the system give more emphasis to scientific merit and less to predetermined program priorities. Thus, a proposal with low program priority (in the opinion of reviewers) but high scientific merit would be given greater funding consideration than a proposal with high program priority but low scientific merit.

The most radical view on peer review may have been expressed by Henry R. Hirsch, PHD, of the Department of Physiology and Biophysics of the College of Medicine, University of Kentucky. He criticized what he said was a reversal of priorities of the researcher who is desperate to get funded.

"He does research in order to get grants," Dr Hirsch said, "when he should be getting grants in order to do research." Speaking as an individual, rather than as a representative of an organization, Dr Hirsch suggested that the peer review system should be scrapped in favor of using the existing university administrative apparatus to distribute whatever funds were targeted by the NIH to that institution. A certain fraction of available funds would be passed through to all researchers on a per capita basis, with the remainder split at the discretion of the administrator in charge. Such discretionary funding might be used to build up a particular department, or for some other reason. Thus, while no one would be impoverished, the most creative and productive researchers would get extra funds.

The range of concerns and opinions expressed at the public hearing might be summarized as being concerned with assuring taxpayers, interest groups, and physicians that the NIH is getting the most out of its research dollars. The obstacles in the way of accomplishing that mission are the difficulty of establishing research priorities, either within an existing institute or by means of establishing a new institute, and the limitations of the peer review system. The advice that the Ebert committee received was extensive and sometimes conflicting. The committee now faces the task of trying to reconcile conflicting interests among the medical, research, political, and private interest groups. The committee's final report, due in October 1984, may be as much of a tight-rope walk as it is a blueprint for the future organization—or reorganization—of the NIH.

Information on the committee and its work can be obtained from Dr Michael Stoto, Institute of Medicine, National Academy of Sciences, 2101 Constitution Ave, Washington, DC 20418; or call (202) 334-2268.

THE NATIONAL INSTITUTES OF HEALTH

The National Institutes of Health were established by Congress in 1930 as part of the Public Health Service Act. The legislation contained no time limits or dollar restrictions on scientific investigations, thus implicitly encouraging basic research. In 1968, the Secretary of the Department of Health, Education and Welfare reorganized the NIH as a separate agency within the Public Health Service.

Since its founding, the NIH has undergone several intramural changes aimed at consolidating specific areas of research. The National Cancer Institute (NCI), formed in 1937, was the first separate institute of the NIH. The National Cancer Act of 1971 accorded the NCI additional funding and gave it high visibility and status within the NIH.

Over the years, other institutes were established within NIH:

1948: National Heart Institute (now called National Heart, Lung and Blood Institute); National Institute for Dental Research; National Microbiological Institute (now the National Institute for Allergy and Infectious Diseases).
1950: National Institute of Arthritis, Diabetes and Digestive Diseases; National Institute of Neurological and Communicative Disorders and Stroke.
1952: National Institute of Child Health and Human Development; National Institute of General Medical Sciences.
1966: National Institute of Environmental Health Sciences.
1968: National Eye Institute.
1974: National Institute on Aging.
1983: National Institute of Arthritis and Musculoskeletal Diseases*

Today, the NIH has 11,400 employees, of whom 1000 have an MD and 1400 have a PHD. The overall budget is $3.5 billion, of which 89% goes to research. The director of the NIH, James B. Wyngaarden MD was formerly the chief of staff of Duke University Hospital, at Duke University School of Medicine.

Information on any aspect of the NIH may be obtained by writing:

Director's Office
National Institutes of Health
Department of Health and Human Services
9000 Rockville Pike
Building 1, Room 124
Bethesda, MD 20205

* Bill authorizing institute passed by House of Representatives; Senate action pending.

Physician involvement in torture

According to *The Lancet* (1983; ii: 584), former prisoners of Chile report that physicians may be involved in administering torture. Evidence of physician involvement includes the way physical examinations are conducted on patients, the use of medical terminology, and medical treatment of patients in two cases in which electrical torture caused respiratory difficulties.

J. L. Gonzalez, MD, the head of the Chilean Medical Association has stated his concern over the matter, but has been unable to ascertain the identity of physicians taking part in torture.

Brian Fisher, MD, a general practitioner in London, has worked closely with Chilean refugees in the United Kingdom and says that they had been deeply traumatized by the torture, either physically or psychologically or both.

Reference on AIDS

AIDS Project/Los Angeles, a nonprofit organization, offers a comprehensive AIDS bibliography free of charge. The volume includes articles through 1982 and a supplement for the first half of 1983. (AIDS Project/Los Angeles, 937 North Cole Avenue, Suite 3, Los Angeles, CA 90038)

Toll-free hotline for drug and alcohol abuse problems

Kiwanis Clubs in New York State have established a toll-free telephone number for parents, relatives, or friends of people with drug problems. The program, called Drugs Today, Gone Tomorrow, is staffed by volunteers who protect the anonymity of callers and advise them on whom to contact in their area. The staff uses lists of agencies published by the state division of Substance Abuse Services and the National Institute on Drug Abuse.

Many of the volunteers are individuals who benefited from the program during their own recoveries from drug dependence.

The toll-free number is (800) 522-5417.

Ohio physicians fill health care gaps

The Ohio State Medical Journal reports (1983; 79: 833–836) that the state legislature is considering a bill that would require certain employer-sponsored group health insurance policies and self-insurance plans to offer group rates to terminated employees for six months. Meanwhile, many Ohio physicians are providing their services to the newly unemployed at reduced rates or no charge.

In December 1982, the Ohio State Medical Association voted to encourage development by county medical societies of programs to provide health care free of charge or at reduced cost to patients who are unemployed, uninsured, and ineligible for Medicaid or other assistance programs.

In response, physicians around the state have since set up programs such as Project Health Concern in Columbus and Project 83 in Cleveland. In its first ten months, Project 83 referred 2,000 patients to 1,500 participating physicians.

The name of the programs vary from city to city. In Toledo is called Academy Med-Assist. In Akron it's Project Summit. And although no formal program exists in Trumbull County, members of the local medical society agreed that they would continue to see patients regardless of their ability to pay.

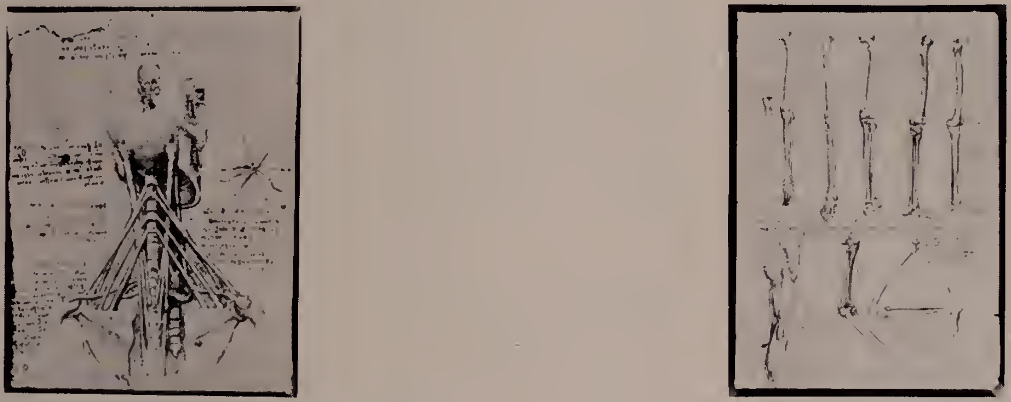
The need for such programs has been great in cities like Toledo, where suppliers to the ailing auto industry have laid off hundreds of workers.

Although the programs across Ohio were started during what was perceived to be a temporary downturn in the economy, economic indicators suggest that high unemployment in Ohio is a long-term problem. Thus, many of the assistance programs may continue to operate indefinitely.

NEWS BRIEFS AND NEWSFEATURES are compiled and written by Marc Kusinitz, PhD.

Leonardo da Vinci Drawings Are Highlight of Exhibition at the Met

"Leonardo da Vinci Anatomical Drawings from the Royal Library, Windsor Castle," and a companion exhibition of 16th Century anatomical prints, "Art and Anatomists," which includes prints that Jan Stephan van Calcar created for the famous anatomy manual *de Humani Corporis Fabrica* by Andreas Vesalius, will run through April 15 at the Metropolitan Museum of Art in Manhattan. The Leonardo exhibit, composed of 50 of the library's 200 anatomical drawings by the artist, records the progression of his thought, observations, and discoveries made from anatomical dissections. In addition to the Jan van Calcar woodcuts, the "Art and Anatomists" exhibition includes Renaissance scenes of dissection theaters and anatomic illustrations by medieval artists that were based on imaginary and vague references to specific organs, muscles, and bone.



The Muscles of the Neck (left, circa 1513) and The Bones of the Leg (1508–1510), are two of Leonardo's anatomical drawings, which were executed in pen and brown ink or red chalk between 1485 and 1515.

These two woodcuts, reprinted from original blocks used to illustrate *de Humani Corporis Fabrica* (1493), are The Weeper (left) and The Philosopher. The New York Academy of Medicine donated them to the museum in 1947.

BIOSTATISTICS IN CLINICAL MEDICINE

By Joseph A. Ingelfinger, MD, Frederick Mosteller, PhD, Lawrence A. Thibodeau, PhD, and James H. Ware, PhD 316 pp. New York, Macmillan Publishing Co., Inc., 1983. $24.95.

The purpose of this text is to apply statistics to problems of medical diagnosis, treatment and follow-up. In the preface, the authors promise to prepare physicians to use and understand applications of probability and statistics in the care of the individual patient. It is a promise not fully kept, in spite of the authors' unusual blend of statistical and medical expertise.

The book is useful to physicians and others who have had some background in statistics and can select those topics that are well presented, of which there are several.

The first three chapters cover decision-making, including topics such as sensitivity, specificity and predictive value of diagnostic tests, revising probabilities, and decision tree analysis. The level of difficulty is probably sufficient to discourage most physician readers from continuing.

Chapters 4–7 discuss material covered in most basic texts in biostatistics, but with a heavy emphasis on clinical applications. The material includes measures of central tendency, variability, the Normal, Student's t-test, the Poisson distributions, confidence intervals, and hypothesis testing. The material is generally useful and well illustrated. However, clinical applications are sometimes emphasized at the expense of describing the procedures utilized.

Chapter 7 deserves special mention. Some extremely important issues are raised, such as the definition of P values, problems of multiple comparison bias, and the meaning and importance of statistical significance versus pratical significance. Unfortunately, the coverage of these topics is uneven. Consider the following quote (p. 161) defining a P value for the observation of three cases of hepatitis in a week, assuming that the average rate is one per week, and the occurrence follows a Poisson distribution: "Notice that the P value is the probability of the result observed or one more extreme, given the hypothesized rate, not the probability the rate is 1 given the data. Confusion about this point often leads to misinterpretation of P values." With such definitions, it is no wonder that there is confusion. Fortunately, the authors repeat important points and highlight them in boxes, which gives the reader several needed opportunities to digest them.

Chapter 8 on chi-square is well done although listed as optional in the preface.

Chapters 9 and 9A on regression analysis are adequate.

Chapters 10 and 11 represent the most important chapters in the book. Chapter 10 deals with interpreting clinical trials, and Chapter 11 applies the results to the individual patient. As with most of the book, the quality of these chapters is uneven. The topics of randomization, "blinding," follow-up and multiple comparison bias are presented well. The issue of imbalance in baseline characteristics between groups is less clearly presented. The appendix to Chapter 10 is an article "Lidocaine in Prevention of Primary Ventricular Fibrillation." The authors use this as a source of questions in Chapters 10 and 11 and provide some brief answers at the end of the book. I found this trial lacking in the apparent absence of informed consent and in any difference in mortality between the groups. These points are either glossed over or not discussed by the authors.

Finally, Chapter 11 applies the results of a random trial, Hypertensive Detection and Follow-up Program, to a 35-year black woman with diastolic blood pressure readings of 94, 98 and 96 on three separate occasions. It concludes that the patient should be treated. This despite the dilemma that subjects less than 50 years showed little improvement, while black women showed substantial improvement. Since there were too few black women to stratify by age, we don't know the trial results for this particular type of patient. The subject could have been placed in either category, (i.e. black women or less than 50 yrs.) with different conclusions as to treatment. The authors seem to base their decision on the result of the overall trial, a reasonable but not particularly satisfying approach.

In summary, this book is not for all physicians. For those with the background who are willing to put in the effort, there are some excellent sections that cannot be found elsewhere.

JOSEPH FELDMAN, DR PH
SUNY Downstate Medical Center
New York City 11203

CONTEMPORARY METABOLISM

Vol 2. Edited by Norbert Freinkel MD, 540 pp., illustrated. New York, Plenum, 1982. $42.50.

In this latest volume of the series formerly entitled, *The Year in Metabolism*, Dr Freinkel, a well-known endocrinologist and student of metabolism, has assembled a series of critical reviews by an impressive panel of experts. Topics covered include selected aspects of diabetes mellitus, the secretion, function, and role of glucagon, hypothalamic pituitary function in obesity, the role of plasma apolipoproteins and lipoprotein receptors in lipoprotein metabolism, alcohol, amino acids and encephalopathy. Also covered are the role and metabolism of gamma-aminobutyric acid and taurine, nutrition and aging, receptors and second messengers in cell function and disease, stimulated phosphatidylinositol turnover, disorders of purine and pyrimidine metabolism, metabolic aspects of urinary stone disease, and metabolism of calcium, phosphorus, magnesium, and vitamin D.

These clinically oriented reviews are clearly written, and the illustrations effectively clarify the text.

Although the most recent references cited are from 1980, the book is an excellent review of the literature to that date.

I recommend this book both to clinical and basic investigators of metabolism and related fields, and to practicing clinicians.

HENRY GODFREY, MD
New York Medical College
Valhalla, NY 10595

A THEORY OF MEDICAL ETHICS

By Robert M. Veatch. New York, Basic Books, Inc. 1981. Hardcover, 387 pages, $20.95.

This book on medical ethics by Robert Veatch addresses an area physicians always deal with, but give little sustained thought to, until faced with an unusually perplexing issue. Professor Veatch uses actual examples to illustrate the difficult decisions doctors often face. Through the author's analysis of these examples, the reader sees the inadequacies of the standard guidelines available.

The author is certainly well qualified to discuss these issues. He was coordinator of the Program on Medical Ethics at Columbia University College of Physicians and Surgeons in the 1970s. He has been a staff member of the Hasting Center, an institution devoted to the study of ethics in the life sciences. At present he is Professor of Medical Ethics at the Kennedy Institute of Ethics, Georgetown University and has published other books on the subject of medical ethics.

The book begins by citing a case history involving a difficult medical problem: A dying patient requests her doctor to provide her with information on how to kill her infant painlessly, because she feels the infant would not adequately survive without her. The analysis of this situation is more complicated ethically than it would at first appear. Professor Veatch examines the Hippocratic tradition and shows that it is not helpful in this, and many other, instances. Other traditions of medical ethics are also delineated and applied to the same dilemma with differing, and often not very helpful, solutions. The traditions examined include the Judaic, Catholic, Protestant, modern secular Western (patient's rights), Socialistic, Islamic, Hindu, Chinese and Japanese.

However, medical ethics involves areas other than the relationship between doctor and patient. There are issues that concern the relationship between doctors and society. As an example of this, the author discusses the medical profession's attempt to prohibit advertising. Also considered are issues of ethics within the profession between organized medicine and the individual physician.

Through analysis of such issues and the questions they raise, the author discusses the mechanisms that would be utilized in formulating an "ideal" moral code. He then considers the philosophical and ethical merits of each of the issues to be part of the code. Throughout this section he makes use of actual and hypothetical life situations and makes many references to scholars in ethical philosophy. In the final section of the book, the author presents an actual code of medical ethics as he would conceive it.

From the point of view of a physician not trained or well grounded in the philosophy of ethics, this book makes for difficult reading. Much of the writing deals with philosophic arguments and references that may be of little interest to the practicing physician. A number of conclusions that are reached might be difficult for the reader to accept: For example, that the physician must tell every patient everything about his diagnosis, treatment and prognosis unless the doctor and patient agree that this is not to be done. While most of the author's conclusions are the result of logical arguments, his decision that doctors should not participate in "mercy killing" is based on his statement "I find the prohibition is one [moral rule] that I must cling to. It is morally an ultimate . . ." The author's conclusion that the rules must be followed for all patients no matter what the circumstances are, will also be unacceptable to physicians who are used to dealing with each patient on an individual basis.

Despite these criticisms, I believe the book is worthwhile for any physician who is concerned with the ethical underpinning of medical practice. It discusses many issues that have often troubled physicians and also raises new issues for consideration.

JULIAN J. CLARK, MD
SUNY Downstate Medical Center
New York City 11203

***Book Review Editor's Note:** Readers are invited to submit reviews of new books. Please contact the Book Review Editor for instructions.*

FOSTER-CHILD HEALTH CARE

By Florence Kavaler PhD and Margaret R. Swire. 195 pp. Lexington, MA., Lexington Books, 1983. $23.95.

This book reports findings of an in-depth, assessment of the health problems and health care experienced by a sample of foster children in New York City during the 1970s. The quality of the research is exceptional in an area noteworthy for paucity of previous scientific investigation. The purposes of the research were to determine relationships between health needs and costs; between organization of medical care employed by foster agencies and its costs, and between organization of medical care and health outcomes.

Clinical examinations provided a comprehensive impression of the physical, dental, and mental-health status of the study children. A medical audit of each child's record was done to identify the pattern, completeness, and adequacy of preventive, diagnostic and treatment services as well as to describe each child's medical history. Process measures included the frequency and completeness of health maintenance visits, immunizations, laboratory and sensory screening status, problem recognition and follow-up practices. Information was gathered regarding sociodemographic characteristics of the study child and his natural and foster family. Also collected were mothers' options of the agency medical program, the availability and accessibility of services, and the state of her and her foster child's health. Finally, refined data are reported concerning medical costs, staffing patterns, clinic schedules and allocation of resources.

Clearly, such a complex study required talented health services researchers. Meticulous attention is given to accuracy and technical detail, particularly readily understood tables and statistical methods. The author's professional backgrounds are impressive. Dr. Kavaler was an Assistant Commissioner for Health and Medical Insurance Programs of the New York City Health Department, where she carried out sentinel medical care evaluations. Her work in subsequent positions confirmed her understandings of administrative public-policy dynamics and sensitivity to community value systems. She currently is a professor of preventive medicine and community health at the State University of New York, Downstate Medical Center. Ms. Swire is a health care consultant with New York Health Research Associates and specializes in the design and implementation of evaluative research. She was director of an earlier foster-child health study and conducted research for the New York City Department of Health on cost control and quality of care in different medical care facilities.

It is not possible even to summarize the immense body of information that the study collected. Several highlights in particular, however, reflect its scope and implications. Twenty-six percent of the children were classified as other than well. At least 45% of the children had a chronic medical illness. Musculoskeletal, congenital malformations, speech and cardiovascular were the most common, with 37% requiring specialty evaluation.

Ten percent were found abnormal on a developmental screening test, another 19% had borderline performances and a random subsample of 179 underwent psychiatric examination, with 70% found to have moderate or severe impairment.

The authors present a lucid, chapter-by-chapter documentation of their findings. Illustrations include the following: (1) children in foster care experienced no more reduction in significant medical and psychiatric problems than those reported for comparable disadvantaged groups; (2) existing delivery systems failed to manage even common child health problems; (3) agencies with high per capita costs had better testing and screening, better record keeping, and higher rates of medical follow through.

Recommendations are explicit, hard-hitting and attainable by a Judeo-Christian society which proclaims a commitment to justice and equality. As the book concludes, ". . . if the responsibility of foster care is not met, the tragedy, not only will be the child's, but also the nation's. Minds and bodies will be lost irretrievably, misplaced and scattered papers, unseen by eyes turned away." Complex sociocultural and political forces determine public policy. But physicians, medical and social service administrators as well as other health professionals will find this "must" reading as they stake out a place for themselves in the caring professions.

EARL SIEGEL, MD
University of North Carolina
School of Public Health
Chapel Hill, North Carolina 27514

A WOMAN IN RESIDENCE: A DOCTOR'S PERSONAL AND PROFESSIONAL BATTLES AGAINST AN INSENSITIVE MEDICAL SYSTEM

By Michelle Harrison, MD 264 pp., New York, Penguin Books, 1983. $5.95.

This book is a good read. The Penguin pocket book edition slips neatly into the pocket of a white lab coat, and probably deserves its place there for a day or two. Although of primary interest to those whose interests would punch into the computer under medical education, women's health care, or quality of medical care, this book of criticism has messages for everyone working in medical academia, or exposed to it from a helplessly horizontal position.

Harrison undertakes an autobiographical account of her six months as a resident in Obstetrics and Gynecology at a major medical center, until the system and her own problems overwhelmed her and she went under. As a single mother of a young daughter, a mature physician ten years into family practice, and a committed advocate of women's health with a totally feminist life style, she entered postgraduate training knowing that it would be an ordeal, and her self-fulfilling prophecy inexorably ended in a book. As we read how the tidal waves of disillusionment and anger washed over her, we can nearly taste the salt in our own mouths.

The writer's outspoken criticisms of the management, personnel, goals and objectives of what she sees as an unnatural and oppressive treatment system, will inevitably polarize readers into those "fer" and those "agin" her position. To some she will appear a cranky, irritable, unfair, hypersensitive, judgmental, holier-than-thou quitter, who washed out and good riddens. To others she will appear a courageous and fragile flower, too devoted to her patients, martyred by an inflexible and sinister health care apparatus, and ultimately crushed by the tyrany she portrays. Psychiatrists will be tempted toward psychobiography, since the author reveals so many of her own raw nerve endings and fairly begs for professionals to analyze the unconscious elements that drove her to this experience, and made it such an ordeal for her.

At the risk of philosophizing unduly, I would point out that to a rare few of us is it given to have a keen eye, a sensitive spirit, a canny ability to see and describe what others take for granted, accept as "given," or blunt with their more highly developed defenses. Although we can dismiss as flawed the criticisms of such people, we do so at our peril. Paranoids spot danger long before the rest of the herd; aesthetes find beauty lost on the masses; creative artists weave tapestries of meaning not heretofore recognized by the rest of us. Buried in the carping and complaints, the projections and self-pity, the false self-doubt, the grim sense of isolation, lie charges that bear close attention. The author's "J'accuse" is valid.

There are technical difficulties to be noted. The book is repetitive and in need of tighter editing. The device of alternating narrative with diary entries causes abrupt changes in tense and mood that are annoying. The point of view is not coherent; long passages of technical descriptions of surgical procedures designed for health education alternate jarringly with poetic descriptions of subjective experiences. There is no discussion of the more global aspects of the problems presented to the reader; there are no attempted resolutions, no critical analyses, no realistic suggestions for alternatives. We have simply had mud thrown upon us and are left to launder ourselves as best we can. It does not endear us to the writer.

The strongest points of the book are the author's candid descriptions of the devastating effects of trying to be a single mother and a sleepless resident; her sly descriptions of verbal ripostes between the legs of anesthetized women; her descriptions of alternative birthing systems that sound tempting even to the most fervent hospitophiles among us.

This book will undoubtedly be purchased by patients who will read, shiver, (gloat, perhaps), and drop it like a half-consumed bird at the feet of their physicians. For this reason, any obstetrician/gynecologist who doesn't bother to read it should have his private parts examined.

NAOMI R. BLUESTONE, MD
North Shore University Hospital
Manhasset, N.Y. 11030

DIFFERENTIAL DIAGNOSIS: ABDOMINAL PROBLEMS

By Fred B. Thomas. 119 pp., illustrated. New York, Arco Publishing, Inc., 1983. $12.00

This book presents a diagnostic approach to various common problems associated with the practice of gastroenterology. Each chapter deals with a particular topic: abdominal pain, abdominal masses, fiberoptic endoscopy, dysphagia, upper gastrointestinal bleeding, portal hypertension, ascites, jaundice, routine examination and analysis of stool, diarrhea, and laboratory evaluation of malabsorption syndromes. In the preface, the authors contend that ". . . little or no attention is directed toward a symptom-oriented approach in the teaching of medicine." This may be true of Ohio State University but I think it unfair to apply this generalization to other institutions. In any case, the authors have written this book in a "symptom-oriented" fashion to attempt to rectify this presumed deficit in current medical education.

The authors, all from the Division of

Gastroenterology at the Ohio State University, appear to have no special qualifications for writing their respective chapters. That is, I do not recognize any of them as an authority in any of these areas nor is investigation by the authors listed in the references accompanying each chapter. Despite this, they have written a concise, relatively up-to-date book that should prove useful to medical students and house officers who are still developing a diagnostic approach to abdominal disease. The book is too superficial to be of much use to fellows in gastroenterology or practicing internists who will probably require more complete works in gastroenterology or hepatology as reference sources.

Each chapter in this book is followed by a brief case presentation, presumably from the author's experience at the Ohio State University, illustrating a clinical problem reviewed in the chapter. This is followed by a series of questions and discussion of the answers to these questions. These case presentations provide an opportunity for the reader to utilize the information provided in the preceding chapter to approach common diagnostic problems.

Although references are given at the end of each chapter, many key statements are unreferenced. For example, it is stated that "several centers have reported remarkable success with colonoscopic identification of acutely bleeding lesions of the colon." Although this statement is true, appropriate references would allow the interested reader to determine the quality of these studies and to define "remarkable success." In general, more references would have improved this book as a source for physicians attempting to learn more about a particular abdominal problem.

I noted few errors in this book, typographical or otherwise. There are, however, some statements of procedure that I disagree with. For example, I am certain that many gastroenterologists would not understand the author's reluctance to do an air-contrast barium enema at once, rather than a routine barium enema and then an air-contrast barium enema, "if necessary," in the investigation of lower gastrointestinal bleeding. Moreover, I would also disagree with the implication that all patients with upper gastrointestinal bleeding must undergo fiberoptic endoscopy. Recent, well-designed studies appear to show no benefit from upper endoscopy in many patients with self-limited episodes of bleeding.

In conclusion, although this book may serve a purpose in the early stages of medical education (ie, medical students and house officers), it is too superficial to be of much use to practitioners. The larger, better-referenced textbooks of gastroenterology will serve their needs much better.

JEAN-PIERRE RAUFMAN, MD
SUNY, Downstate Medical Center
New York City 11203

SKIN PROBLEMS OF THE AMPUTEE

By S. William Levy, MD 304 pp., illustrated. St. Louis, MO., Warren H. Green, 1983. $49.95.

Prior to my being asked to review *Skin Problems of the Amputee* by S. William Levy MD, I had a patient in the office with a complaint of inflammation and dermatitis of her stump. Additionally, she had diabetes. The leg had been amputated following a car accident when she was in her twenties. I realized that there was very little on this subject in the standard dermatological texts available to physicians.

S. William Levy MD has devoted over 30 years to the problems of the amputee. His considerable experience was enhanced by a 12-year research project by the Dermatology Study Group at the Biomechanics Laboratory at the University of California in San Francisco. This involved the collaboration of dermatologists, orthopedists, engineers and prosthetists.

Indeed, this book is written for readers of various interests and discusses the anatomy of bone and skin and the structure and functions of the lower limb. The book is exclusively about amputation of the leg. There are numerous clear figures and photographs. The appendix includes patient visual aids reproduced from a pamphlet. Approximately, 110 pages are devoted to the special effects of the prosthesis on the skin and include discussions of mechanical injury, epidermoid cysts, contact dermatitis and circulatory disorders of the stump. Additionally, bacterial, viral and fungus infections are presented. Dr Levy also reviews some of the benign and malignant tumors of the stump skin.

Skin Problems of the Amputee is an excellent monograph and may be unique. It can be read by anyone who must care for the more than 300,000 amputees in the United States. Dr S. William Levy has written a knowledgeable monograph.

HANS F. KIPPING, MD
Erie County Medical Center
Buffalo, N.Y. 14215

In addition to these listings, the Journal *welcomes obituaries written by physician readers. Inquiries should first be made to the Editor.*

Robert Winsper Angevine, MD, Rochester. Died October 24, 1982; age 89. He graduated in 1918 from Harvard Medical School and was a member of the Medical Society of the County of Monroe and the Medical Society of the State of New York.

Simon Roberto Bakall, MD, Poughkeepsie. Died July 25, 1983; age 67. He graduated from the University of the Philippines College of Medicine, Manilla Philippines in 1940. Dr. Bakall was a Fellow of the American College of Anesthesiologists, and a member of the American Society of Anesthesiologists, the New York State Society of Anesthesiologists, the Dutchess County Medical Society, and the Medical Society of the State of New York.

Robert Middlebrook Bogue, MD, Rochester. Died August 14, 1983; age 72. He graduated from the New York University College of Medicine in 1937 and was a member of Nassau County Medical Society and the Medical Society of the State of New York.

Philip Brown, MD, Bronx. Died April 30, 1983; age 85. Dr. Brown graduated in 1926 from New York University College of Medicine and was a member of the Bronx County Medical Society and the Medical Society of the State of New York.

Daniel H. Casriel, MD, New York City. Died June 7, 1983; age 59. Dr. Casriel graduated in 1949 from the University of Cincinnati College of Medicine. His memberships included the New York County Medical Society and the Medical Society of the State of New York.

Salvatore G. Cinque, MD, Pelham Manor. Died April 29, 1983; age 62. He graduated in 1946 from Stritch School of Medicine of Loyola University. His memberships included the New York County Medical Society and the Medical Society of the State of New York.

Burrill B. Crohn, MD, New York. Died July 29, 1983; age 99. Dr. Crohn graduated in 1907 from Columbia University College of Physicians and Surgeons. He was a member of the Academy of Medicine, the American Gastroenterological Association, the American Society of Colon and Rectal Surgeons, the New York County Medical Society, and the Medical Society of the State of New York. Dr. Crohn was a Fellow of the American College of Physicians and a Diplomate of the American Board of Internal Medicine.

Aron Jacob Deutscher, MD, Bronx. Died July 30, 1983; age 79. Dr. Deutscher graduated from the Deutsche Universitat Medizinische Fakultat, Prague, Czechoslovakia in 1934. He was a member of the Bronx County Medical Society and the Medical Society of the State of New York.

William Dailey Dunaway, MD, New York City. Died December 26, 1983; age 81. In 1930 he graduated from the University of Louisville School of Medicine. Dr. Dunaway was a member of the New York County Medical Society and the Medical Society of the State of New York.

Isadore Givner, MD, New York City. Died December 14, 1982; age 79. Dr. Givner graduated in 1926 from the Medical College of South Carolina and was a member of the New York County Medical Society and the Medical Society of the State of New York.

Zalman Grinberg, MD, Seaford. Died August 7, 1983; age 71. Dr. Zalman graduated from the Universitat Basel Medizinische, Fakultat, Switzerland in 1938. He was a member of both the Nassau County Medical Society and the Medical Society of the State of New York.

Francis Joseph Gustina, MD, Buffalo. Died July 22, 1983; age 82. Dr. Gustina graduated in 1925 from the University of Buffalo School of Medicine and was a member of the Medical Society of the County of Erie and the Medical Society of the State of New York.

Argus Bernard Haley, MD, Eggertsville. Died August 2, 1983; age 61. He was graduated from Marquette University School of Medicine in 1946. His memberships included the Medical Society of the County of Erie and the Medical Society of the State of New York.

William Alexis Hamilton, MD, Newark, NJ. Died July 18, 1983; age 69. He was a 1940 graduate of the University of Pennsylvania School of Medicine. Dr. Hamilton was a member of the Medical Society of the County of Wayne and the Medical Society of the State of New York.

William Maxwell Hitzig, MD, New York City. Died August 27, 1983; age 79. He graduated in 1929 from Cornell University Medical College. Dr. Hitzig was a member of the New York County Medical Society and the Medical Society of the State of New York.

Daniel Hyman, MD, Suffern. Died July 24, 1983; age 72. He was graduated from Licentiate of the Royal College of Physicians of Edinburgh, Scotland in 1937. Dr. Hyman was a Diplomate of the American Board of Preventive Medicine, Inc. and the American Board of Dermatology, Inc. He was a Fellow of the American College of Preventive Medicine and his memberships included the Society for Investigative Dermatology, the American Academy of Dermatology, the New York State Dermatological Society, the Academy of Medicine, the Medical Society of the County of Rockland, and the Medical Society of the State of New York.

Paul L. Jones, MD, Sag Harbor. Died August 15, 1982; age 81. Dr. Jones graduated from Tufts University School of Medicine in 1927. His memberships included the Medical Society of the County of Kings and the Medical Society of the State of New York.

Chester J. Kaminski, MD, Elma. Died July 6, 1983; age 69. He graduated in 1938 from the University of Buffalo School of Medicine. Dr. Kaminski was a Fellow of the American College of Surgeons, a Diplomate of the American Board of Obstetrics and Gynecology, a member of the Medical Society of the County of Erie, and the Medical Society of the State of New York.

Seymour M. Katz, MD, New York City. Died August 18, 1983; age 71. He was graduated from the Albany Medical College of Union University in 1935. His memberships included the New York County Medical Society and the Medical Society of the State of New York.

Israel Kaufman, MD, Brooklyn. Died February 18, 1983; age 84. He was graduated from the University of Maryland School of Medicine in 1928. His memberships included the Medical Society of the County of Kings and the Medical Society of the State of New York.

Gino Joseph Laudi, MD, Brooklyn. Died April 22, 1983; age 69. Dr. Laudi graduated from the Universita Degli Studi Di Roma, Facolta Di Medicina e Chirurgia, Italy in 1943. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Pasquale J. Laviano, MD, Bellport. Died August 3, 1983; age 77. He graduated from the Universita Degli Studi Di Roma, Facolta Di Medicina e Chirurgia, Italy in 1933. Dr. Laviano was a member of the Suffolk County Medical Society and the Medical Society of the State of New York.

Joseph Harold Merin, MD, Rochester. Died June 15, 1982; age 78. Dr. Merin graduated in 1927 from Cornell University Medical College. His memberships included the New York County Medical Society and the Medical Society of the State of New York.

Charles Werner Mueller, MD, Cincinnati, Ohio. Died August 9, 1983; age 85. He was graduated from Ohio State University College of Medicine in 1924 and his memberships included the Medical Society of the County of Kings and the Medical Society of the State of New York.

Louis Z. Pampellonne, MD, Bethpage. Died August 25, 1983; age 64. He graduated in 1951 from Columbia University College of Physicians and Surgeons and was a member of the Nassau County Medical Society and the Medical Society of the State of New York.

Edwin Rand Reynolds, MD, Rochester. Died July 14, 1983; age 97. He was graudated from the University of Michigan Homeopathic Medical School in 1912. Dr. Reynolds was a member of the Medical Society of the County of Monroe and the Medical Society of the State of New York.

Joel Robbins, MD, East Meadow. Died August 15, 1983; age 57. Dr. Robbins graduated from the Universite De Lausanne Faulte De Medecine, Switzerland in 1959. He was a member of the Nassau County Medical Society and the Medical Society of the State of New York.

Edward H. Roston, MD, Hewlett. Died August 29, 1873; age 64. In 1943 he graduated from Columbia University College of Physicians and Surgeons. He was a member of Nassau County Medical Society and the Medical Society of the State of New York.

Joseph Safian, MD, Miami Beach. Died July 20, 1983; age 97. Dr. Safian graduated from the State University of New York Downstate Medical Center in 1907. His memberships included the New York County Medical Society and the Medical Society of the State of New York.

Victor Saunders, MD, New City. Died April 30, 1983; age 61. He graduated from the Universitat Bern Medizinische, Fakultat, Switzerland in 1963. His memberships included the Medical Society of the County of Rockland and the Medical Society of the State of New York.

Edward Singer, MD, Stillwater, NJ. Died November 9, 1982; age 81. He graduated from Friedrich-Wilhelms Universitat Med Fakultat, Berlin, Prussia, Germany in 1926. He was a member of both the Medical Society of the County of Kings and the Medical Society of the State of New York.

Bernard Strauss, MD, New York City. Died July 29, 1983; age 72. Dr. Strauss graduated from the State University of New York Downstate Medical Center (Long Island College of Medicine) in 1935. He was a member of the New York County Medical Society and the Medical Society of the State of New York.

Sidney Thier, MD, New York City. Died April 10, 1983; age 72. He was graduated from the State University of New York Downstate Medical Center (Long Island College of Medicine) in 1936. His memberships included the Medical Society of the County of Kings and the Medical Society of the State of New York.

Russel J. Van Coevering, MD, Buffalo. Died January 1, 1982; age 57. He graduated from the University of Buffalo School of Medicine in 1949 and was a member of the Medical Society of the County of Erie and the Medical Society of the State of New York.

Alfred H. Viessmann, MD, St. Augustine, FL. Died July 23, 1983; age 87. Dr. Viessman graduated from Ludwig-Maximilians Univ Med Fakultat, Munchen, Bavaria, Germany in 1923 and was a member of the Suffolk County Medical Society and the Medical Society of the State of New York.

Raymond L. Vande Wiele, MD, Alpine, NJ. Died August 14, 1983; age 54. He graduated from the Universite Catholique De Louvain Faculte De Medecine in Belgium in 1947 and was a member of both the New York County Medical Society and the Medical Society of the State of New York.

James Raymond Wilson, MD, Sylvan Beach. Died August 17, 1983; age 77. Dr. Wilson graduated in 1934 from Duke University School of Medicine. He was a member of the Medical Society of the County of Madison and the Medical Society of the State of New York.

Samuel Zwerling, MD, Woodbury. Died August 12, 1983; age 89. He was graduated from the State University of New York Downstate Medical Center (Long Island College Hospital) in 1916 and was a member of Nassau County Medical Society and the Medical Society of the State of New York.

Guidelines for authors

ORIGINALITY

The *New York State Journal of Medicine* welcomes research papers and original essays on the practice of medicine, medical education, public health, the history of medicine, medicolegal matters, legislation, ethics, the mass media and socioeconomic issues in health care.

Manuscripts should be prepared according to the "Uniform requirements for manuscipts submitted to biomedical journals," (*NY State J Med* 1983; 83:1089-92. The requirements were established by the International Committee of Medical Journal Editors, of which the *Journal* is a participating member. These Guidelines are intended to highlight aspects of the *Journal's* particular style of publication.

A manuscript will be considered for publication if it is original, has not been published previously in whole or in part in either a medical journal or a lay publication, and is not simultaneously under consideration elsewhere. A copy of any possibly duplicative material, such as a reference "in press," should be submitted along with the manuscript.

PREPARATION

An original typewritten or "word-processed" manuscript and two photocopies (to facilitate outside review) are required. If the manuscript is not accepted for publication, the original and one copy will be returned. All figures must be submitted in triplicate. The manuscript should be double-spaced throughout, including references, tables, legends, quotations, and acknowledgments. A separate title page should include the full title of the paper in upper and lower case type, the names of the authors exactly as they should appear in print (including their highest academic degree), an abbreviated title of no greater than 40 spaces for use as a running foot, and the names of all providers of funding for research on which the paper is based. Information on the amount and allocation of funding is optional.

A corresponding author should be designated in the covering letter. Authors should list their title and affiliation at the time they did the work, and, if different, their present affiliation. The addresses and telephone numbers of all authors should be supplied for editorial purposes. All authors of a manuscript are responsible for having read and approved it for submission.

CATEGORIES

Research Papers should be limited to 2,500 words and should include the following sections: Introduction, Methods, Discussion, and References. Multiple subheadings and numbered lists are discouraged. An abstract limited to 150 words should state the reasons for the study, the main findings, and their implications. Statistical evaluations should be described in the Methods section, and the name and affiliation of the statistician should be included in the acknowledgments if this individual is not listed as a coauthor. Reports of experiments involving human subjects must include a description in the Methods section of the informed consent obtained and a statement that the procedures followed were approved by an institutional research review committee. Anonymity of patients must be preserved. Reports of experiments on animals must note which guidelines were followed for the care and use of laboratory animals.

Preference will be given to Case Reports limited to 1,250 words. Review Articles should not exceed 3,000 words. Commentaries should be between 750 and 1,000 words. Other kinds of original essays should not exceed 2,000 words. A letter of inquiry should be sent to the editor prior to submitting a Review Article or Commentary.

For Research Papers only, scientific measurements should be given in conventional units, with Système Internationale (SI) units in parentheses. Abbreviations and acronyms should be kept to a minimum, and jargon should be avoided. Generic names of drugs should be used instead of brand names.

FIGURES

The submission of color illustrations or slides is discouraged. Only black and white glossy photographic prints or "camera-ready" artwork will be accepted. The *Journal* is unable to provide art services such as the addition of arrows to photographs. A signed consent for publication must accompany photographs in which the patient is identifiable. Illustrations from other publications generally will not be considered. Legends for illustrations should be typed on a separate sheet, and for photomicrographs should include magnification and stain. Each illustration should be lightly marked on the back in pencil with the name of the first author, the number as cited in the text, and an arrow indicating the top. Each set of illustrations should be submitted unmounted in a separate envelope.

Tables should be simple, self-explanatory, and few in number. Each table should be typed double-spaced on a separate sheet.

REFERENCES

References should be limited to the most pertinent. The recommended maximum number of references is 25 for Research Papers and most other original contributions (except lengthier Review Articles), 12 for Commentaries and Case Reports, and 6 for letters to the editor.

Authors are responsible for the accurate citation of references. Citation of secondary sources is discouraged except where the original reference is unobtainable. Authors may not cite references they have not read, and the use of abstracts as references should be avoided.

References should be indicated in the text by superscript numbers following the name of the author (eg, Smith^2 reported two cases).

The list of references at the end of the article should be typed double-spaced and references should be numbered in the order in which they appear on the text. When there are six or fewer authors, all should be listed; where there are seven or more, the first three should be listed, followed by *et al.* Names of journals should be abbreviated according to *Index Medicus* and underlined.

Sample references:

1. Kepes ER, Thomas P, Vemulapalli K: Methadone and intravenous morphine requirements. *NY State J Med* 1983; 83:925-927.
2. McGuigan JE. Peptic ulcer. In: Petersdorf RG, Adams RD, Braunwald E, Isselbacher KJ, Martin JB, Wilson JD, eds. *Harrison's Principles of Internal Medicine.* New York, McGraw-Hill, 1983, pp 1697-1712.

REVIEW

All manuscripts are reviewed by the editors, and most manuscripts are sent to outside referees. Decisions concerning acceptance, revision, or rejection of a manuscript are usually made within three to six weeks. Every effort will be made to assure prompt publication of an accepted manuscript. A copyedited version will be sent to the author for approval prior to publication.

Address correspondence to Alan Blum, MD, Editor, *New York State Journal of Medicine*, P.O. Box 5404, 420 Lakeville Road, Lake Success, NY 11042.

MEDICAL SOCIETY

of the

STATE OF NEW YORK

BYLAWS

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MEDICAL SOCIETY OF THE STATE OF NEW YORK
420 LAKEVILLE ROAD
LAKE SUCCESS, NEW YORK 11042

MEDICAL SOCIETY OF THE STATE OF NEW YORK

BYLAWS

Revised 1983

ARTICLE I. NAME AND PURPOSE

The name and title of the State Society shall be the Medical Society of the State of New York. The purposes of the State Society shall be: to federate into one organization the medical profession of the State of New York; to extend medical knowledge and advance the science and art of medicine; to establish the *Principles of Professional Conduct* which shall be binding on the members of the Medical Society of the State of New York, the members of the component county medical societies, and the members of the component district branches, in all matters in their relation to each other and to the public; to enhance the delivery of medical care of high quality to all people in the most economical manner; to promote the betterment of community health; and to enlighten and direct public opinion in regard to the problems of medicine and health for the best interests of the people of the State.

ARTICLE II. MEMBERSHIP

SECTION 1. CLASSES

The membership in the Medical Society of the State of New York shall be divided into five classes: (a) active, (b) life, (c) honorary, (d) resident, and (e) student.

Active membership shall be limited to graduates of recognized medical or osteopathic schools who have completed not less than four satisfactory years of at least eight months each, or the equivalent, in a medical or osteopathic school in the United States of America or Canada registered as maintaining at the time a standard satisfactory to the medical or osteopathic licensing authorities of the State of New York, or in a medical or osteopathic school in a foreign country maintaining a standard not lower than that prescribed for medical schools in this State.

The active members shall be all active members in good standing of the component county medical societies. A copy of the roster of such members, certified to be correct by the respective secretary of each component county medical society, shall be evidence of the right of the members whose names appear therein to membership in the Medical Society of the State of New York.

Student members shall be those members enrolled in recognized medical or osteopathic schools in the State of New York who are pursuing a course of study leading to the degree of Doctor of Medicine or Doctor of Osteopathy. Eligible students may become members of the Medical Society of the State of New York. Concurrent membership in a component county society and the American Medical Association is not a requirement for student membership. They shall apply for student membership on a form supplied by the secretary together with such dues as are fixed by the House of Delegates. When a student member ceases to be enrolled in a recognized school of medicine or school of osteopathy in the State of New York pursuing a course of study leading to a degree of Doctor of Medicine or Doctor of Osteopathy, other than by reason of graduation, he shall be considered to have resigned from membership in the Medical Society of the State of New York.

A student member who is suspended from the rights and privileges of his medical or osteopathic school shall likewise be suspended for the same period from the Medical Society of the State of New York.

An active member in good standing who has completely withdrawn from the active practice of medicine and who has been a member in good standing for the ten consecutive years prior to the age of sixty-five years or an active member in good standing who continues the active practice of medicine and who has been a member in good standing for the ten consecutive years prior to the attainment of the age of seventy years, or an active member in good standing for ten consecutive years or more who is permanently disabled, may apply for life membership. The House of Delegates or the Council may waive the requirements in a proper case where there appear to be extenuating circumstances. He shall apply for such life membership to the component county medical society of which he is a member. His application shall be governed by the constitution and bylaws of the component county medical society relative to active membership.

His application shall be signed by the president and the secretary of the component county medical society of which he is a member and sent to the secretary of the State Society for presentation to the Council for approval.

The honorary members of the Medical Society of the State of New York shall be such distinguished physicians residing outside the State of New York as may be elected. Nominations for honorary membership shall be endorsed by three members of the State Society and forwarded to the secretary of the State Society for presentation to the House of Delegates. A two-thirds vote of the House of Delegates present and voting shall be necessary for election to honorary membership.

Resident membership shall be limited to graduates of recognized medical or osteopathic schools who are in continuous residency training and who are resident members of a component county medical society. Any resident who is unable to join the component county society (societies) notwithstanding the provisions of Article XVIII, Section 2, paragraphs 5 and 6 of these Bylaws shall be eligible to join the Medical Society of the State of New York directly as a resident member.

This provision shall not affect the status of any individual currently in continuous residency training who became a member of a component county medical society prior to October, 1981.

SECTION 2. PRIVILEGES

Active members vote and hold office in the Medical Society of the State of New York.

They shall be entitled to receive the *New York State Journal of Medicine*, the *News of New York*, and the *Medical Directory of New York State*.

Life members shall not be subject to Medical Society of the State of New York dues or assessments but shall be accorded all the rights and privileges of active membership. They shall be entitled to receive the *New York State Journal of Medicine* and the *News of New York*, but the *Medical Directory of New York State* only on request.

Student members shall be entitled to receive the *News of New York*. Each student member shall only be entitled to receive the *New York State Journal of Medicine* upon his individual written request, on an annual basis. Student members shall not be entitled to receive the *Medical Directory of New York State* free of charge. In addition, student members shall be entitled to the rights and privileges otherwise accorded in these Bylaws to students.

The dues and assessments of resident members shall be no more than one tenth the amount levied on all other active members. The resident members shall be accorded all the rights and privileges of active membership. They shall be entitled to receive the *Medical Directory of New York State* only on request.

Honorary members shall be entitled to the privilege of attending the meetings of the Medical Society of the State of New York.

For a member elected after October 1, all rights and privileges of membership shall date from the time of election.

State Society dues and assessments of a member elected after October 1 shall be credited to the succeeding year.

A member of one component county medical society shall not be permitted to transfer to membership in another component county medical society until he has paid the current annual dues and assessments to the former component county medical society and has established a legal residence or practices in the county to which he desires transfer, except as provided in Article XVIII, "Component County Medical Societies," Section 2. The question of legal residence or locus of practice shall be verified by the component county medical society to which the member desires transfer.

Any member, except a member who is eligible and has applied for life membership, whose component county medical society and Medical Society of the State of New York dues are unpaid after April 1 of any current year or whose assessments are unpaid by the specified time is not in good standing and shall be deemed to be in arrears.

A member of the Medical Society of the State of New York who is in arrears for component county medical society dues and State Society dues or assessments shall not be eligible for any office or delegacy or be entitled to vote for any officer, councilor, trustee, or delegate.

A member whose dues are unpaid after May 1 or whose assessments are unpaid one month after the specified date shall be dropped from the rolls of membership of his component county medical society and the Medical Society of the State of New York upon reasonable notice to such member by his component county medical society, or the State Society, and without further action on the part of either the component county medical society or the State Society; and on such date he shall automatically cease to be a member of both the component county medical society and the State Society. In the case of nonpayment of dues, the reasonable notice to be provided shall commence on April 1, or as soon as possible thereafter, upon the determination that such member is in arrears.

A member who has been dropped from the roll of a component county medical society by reason of failure to pay dues shall not be accepted by another component county medical society except by regular transfer after reinstatement in the original component county medical society.

Medical Society of the State of New York dues of a member reinstated after October 1 shall be credited to the succeeding year, all rights and privileges of membership, however, dating from the time of reinstatement; but no member dropped for nonpayment of dues and assessments shall be reinstated until he has, in addition, paid his dues and assessments for the year in which he was dropped.

A member convicted in a court of law of a crime evidencing moral turpitude shall thereupon cease to be a member of the Medical Society of the State of New York.

A member expelled from his component county medical society or suspended from its rights and privileges shall likewise be expelled or suspended for the same period from the Medical Society of the State of New York. The right of appeal to the State Society shall not be impaired. Members not in good standing or ceasing to be members of their component county medical society shall *ipso facto* have the same status in the State Society.

SECTION 3. CONTINUING MEDICAL EDUCATION

An active member who fails to fulfill the requirements for continuing medical education established by the Council of the Medical Society of the State of New York shall not be in good standing. This section shall become effective on March 1, 1981.

An active member as defined in Article II, Section 1, who is found not to be in good standing as of March 1, 1981, or March 1 of any subsequent year, for failing to comply with paragraph 1 of this Section shall receive reasonable notice that he must fulfill continuing medical education requirements by the last day of December of the year in which he is found not to be in good standing. An active member who does not fulfill continuing medical education requirements by the last day of December of the year in which he is found not to be in good standing shall automatically cease to be a member of the component county medical society and the State Society, unless, in the view of the Council, specific mitigating circumstances exist that the physician could not complete the CME requirements.

ARTICLE III. HOUSE OF DELEGATES

There shall be a House of Delegates which shall be the legislative body of the Medical Society of the State of New York and shall be charged with the general management, superintendence, and control of the State Society and its affairs, and shall have such general powers as may necessarily be incident thereto, except as otherwise specifically provided by the Bylaws.

SECTION 1. COMPOSITION

The House of Delegates shall be composed of: (a) duly designated delegates from the component county medical societies; (b) officers of the Medical Society of the State of New York, councilors, and trustees; (c) a duly designated delegate from each district branch; (d) a duly designated delegate from each recognized specialty society; (e) duly designated delegates from the student membership; (f) the Commissioner of Health of the State of New York, or a deputy designated by him, provided that any representative shall be a member of the State Society; (g) past-presidents of the State Society and any past president of the American Medical Association, provided that individual is a member of the Medical Society of the State of New York who shall be members for life; (h) a representative from each of the medical schools in New York State, provided said representative is a member of the Medical Society of the State of New York; (i) a delegate representing the resident membership and (j) a delegate representing the hospital medical staff section.

The number of delegates to which each component county medical society is entitled shall be determined by one of the two following optional methods:

(a) Each component county medical society shall be entitled to as many delegates as there shall be State assembly districts in such county at the time of election, but each county medical society shall be entitled to elect at least 1 delegate;

(b) Any component county medical society, which according to the rolls of the Medical Society of the State of New York two months prior to the annual meeting, shall have had up to 99 members, shall be entitled to 1 delegate. Any component county medical society having 100 to 199 members shall be entitled to 2 delegates. Any component county medical society having 200 to 349 members shall be entitled to 3 delegates. Any component county medical society having 350 to 499 members shall be entitled to 4 delegates. Any component county medical society having 500 to 749 members shall be entitled to 5 delegates. Any component county medical society having 750 to 999 members shall be entitled to 6 delegates. Any component county medical society having 1,000 or more members shall be entitled to at least 7 delegates and 1 additional delegate for each additional 300 members. Each component county medical society shall be entitled to designate at least 1 delegate, but no component county medical society shall be entitled to designate more than 30 delegates.

A delegate to the House of Delegates shall not be considered in good standing or entitled to vote in the House of Delegates if the component county medical society by which he was elected is in default of the payment of any dues or assessments imposed by the House of Delegates, and said component county medical society has been duly notified of such default, or if such component county medical society shall at the time be under sentence of suspension imposed by the House of Delegates, or if such delegate is not in good standing in the Medical Society of the State of New York, or in the component county medical society to which he belongs.

The term of a delegate duly designated by a component county medical society, district branch, specialty society, medical school or the student membership, shall begin at the first annual meeting of the House of Delegates subsequent to his designation.

A delegate shall practice or maintain residence or an office in the State of New York. Otherwise his office as a delegate in the Medical Society of the State of New York shall be declared vacant by the Council.

The student members of each medical school in New York State shall, at least sixty days prior to the annual meeting of the House of Delegates of the Medical Society of the State of New York, elect two members from among their number to represent them at the business meeting of the student members which shall be held immediately prior to the convening of the House of Delegates. At such meeting the representatives shall elect a chairman, vice-chairman, secretary, delegates, and alternate delegates. The medical student membership shall be entitled to one delegate and one alternate delegate and, according to the rolls of the Medical Society of the State of New York, sixty days prior to the annual meeting, one additional delegate for each additional 400 student members, up to a maximum of 3 delegates. No member shall hold more than one such office. The chairman, vice-chairman, and secretary shall conduct the business meeting and the delegates and alternate delegates shall represent the student members at the first annual meeting of the House of Delegates subsequent to their designation.

The resident membership shall be entitled to elect one delegate to the House of Delegates. The method of electing the resident membership delegate shall be determined by the Council.

SECTION 2. DUTIES

The House of Delegates formulates policy for the Medical Society of the State of New York. No officer, councilor, board, commission, committee, or employee shall initiate any policy or commit the State Society to any policy unless such policy has been expressly approved by the House of Delegates or by the Council.

It shall elect the officers, councilors, and trustees of the State Society and the delegates to the American Medical Association. A student member of the Medical Society of the State of New York, who is in good standing, is eligible for election as delegate to the American Medical Association, provided he is a member of the AMA.

Credentials signed by the president and secretary shall be issued to delegates to the American Medical Association.

It shall pass on the credentials and qualifications of delegates and shall decide who are entitled to be members of the House of Delegates of the Medical Society of the State of New York.

It shall have authority and power to suspend or otherwise discipline its own members, district branches, component county medical societies, or any members of the Medical Society of the State of New York charged with special duties for and under authority of the State Society.

It shall provide for the organization of the district branches; for rules and regulations for its own government, and for the administration of the affairs of the State Society.

It shall provide for the issuance of charters to component county medical societies in affiliation with the Medical Society of the State of New York.

It shall have authority to appoint special committees from among members of the Medical Society of the State of New York.

SECTION 3. MEETINGS

The annual meeting of the Medical Society of the State of New York and the annual meeting of the House of Delegates shall be held at the call of the speaker.

The sessions of the House of Delegates may be adjourned from time to time as may be necessary. At least 30 days before the annual meeting of the House of Delegates, the speaker shall announce a schedule of the adjourned sessions of the House of Delegates. This schedule may be amended by the House of Delegates during its meeting.

Resolutions may be submitted to the House of Delegates only by members of the House of Delegates as individuals, or by component county medical societies, district branches, specialty society delegates, the hospital medical staff delegate, the resident membership delegate, student membership delegates, and medical school delegates.

No new resolution shall be introduced at the last scheduled session except by a unanimous vote of the House of Delegates.

Special meetings of the House of Delegates shall be called by the speaker on the request in writing by 25 percent of the duly accredited delegates of the previous annual meeting of the House, or at the request of the Council; and in case of the failure, inability, or refusal of the speaker to act, such meetings may be called by a notice thereof subscribed by 25 percent of duly accredited delegates.

The notices of the annual and special meetings of the House of Delegates shall state the date, place, hour, and items of business that will be considered. These shall be mailed first class postpaid to each delegate not less than ten nor more than fifty days before such a meeting.

Publication of the notice of the annual meeting in the official publication of the Medical Society of the State of New York shall be considered as complying with this provision.

The affidavit of mailing by the secretary of the Medical Society of the State of New York to the last recorded address of the delegate shall be deemed sufficient proof of the service on each and every delegate for any and all purposes.

A quorum shall consist of 100 members of the House of Delegates.

The following shall be the order of business at the sessions of the House of Delegates:

1. Calling the meeting to order
2. Invocation
3. National Anthem
4. Report of Reference Committee on Credentials
5. Report by the secretary as to the presence or absence of a quorum
6. Remarks by the speaker
7. Reading of the minutes of the previous meeting by title
8. Address by the president
9. Report of House Committee on Bylaws
10. Report of the Judicial Council
11. Reports of Council commissions and committees
12. Report of the secretary
13. Report of the treasurer
14. Report of the Board of Trustees
15. Report of the executive vice-president
16. Reports of district branches
17. Reports of special committees
18. Reports of reference committees
19. Elections
20. Recess for annual meeting of the State Society
21. Unfinished business
22. New business
23. Adjournment

This order of business may be altered by the speaker with the approval of the House of Delegates and may be suspended by two-thirds vote of the House.

No delegate shall speak on any question before the House of Delegates for longer than five minutes nor more than once on any subject except by the consent of a majority vote of the House.

As the first business of the last scheduled session of the annual meeting of the House of Delegates, the officers, councilors, and the trustees of the Medical Society of the State of New York, and the delegates to the American Medical Association shall be nominated and elected.

The rules contained in *Sturgis Standard Code of Parliamentary Procedure* shall govern the House of Delegates in all cases in which they are not inconsistent or in conflict with the Bylaws of the Medical Society of the State of New York or the standing or special rules of the House of Delegates.

ARTICLE IV. COUNCIL

There shall be a Council which shall exercise all the rights and duties of the House of Delegates, consistent with the Bylaws of the State Society, when the House of Delegates is not in session. The Council, therefore, is in fact the executive committee of the House of Delegates.

SECTION 1. COMPOSITION

The Council shall be composed of the president, president-elect, vice-president, immediate past-president, secretary, assistant secretary, treasurer, assistant treasurer, speaker, vice-speaker, chairman of the Board of Trustees, and 12 councilors elected by the House of Delegates.

The trustees, the executive vice-president, the deputy executive vice-president, and the general counsel of the Medical Society of the State of New York shall attend all meetings of the Council with voice but without vote.

Four councilors shall be elected annually by the House of Delegates, each for a term of three years. In the event of a vacancy, a councilor shall be elected by the Council to serve until the next meeting of the House of Delegates, at which time the House of Delegates shall elect a councilor to fill the unexpired term.

No person shall serve, consecutively, more than two terms as councilor. An unexpired term shall not be construed as a term of office.

The councilors shall assume office on election and shall hold office until their successors are duly elected and qualified.

Councilors shall be assigned to specific county societies as liaison for the Council in accordance with the provisions of Article V, Section 2. Councilors shall be required to disseminate information of Council activity as well as returning information to the Council, and shall report regularly to the Council on their activity.

A councilor shall practice or maintain a residence or an office in the State of New York. Otherwise his position in the Medical Society of the State of New York shall be declared vacant by the Council.

If a councilor is absent from three consecutive regular meetings of the Council without proper excuse, the Council shall declare his position vacant and elect a successor for the unexpired term.

SECTION 2. DUTIES

The Council shall take such action as is necessary to carry out the Bylaws and to give full effect to any resolution or vote of the House of Delegates.

It shall also have power to legislate as a House of Delegates, when the latter is not in session, on all matters consistent with the Bylaws.

It shall have the authority to make policy for the Medical Society of the State of New York when the House of Delegates is not in session.

The Council's resolutions and actions shall be decisive and final except that all resolutions and actions of the Council are subject to review by the House of Delegates. Its actions shall be governed by the Bylaws of the Medical Society of the State of New York and the rules and regulations of the House of Delegates.

The Council shall have the authority to vote all funds of the Society subject to the approval of the Board of Trustees.

Should the Board of Trustees disapprove of the expenditure of any funds voted for by the House of Delegates or the Council, then and in that event, the Board of Trustees shall return the matter to either the House of Delegates or the Council, if the House of Delegates is not in session, which may override such disapproval by a three-quarter vote and direct the expenditure of such funds. The Board of Trustees shall not vote on this issue at a meeting of the House of Delegates and the chairman of the Board of Trustees shall not vote on this issue at the Council.

The Council shall have power to fill any vacancy which may occur in any elective office not otherwise provided for, until the next meeting of the House of Delegates.

The Council shall, by written notice, inform the component county medical societies of the specific Councilor assigned to it as liaison with the Council.

It shall prepare an annual budget for submission to the Board of Trustees.

The Council utilizing a search committee shall, with the approval of the Board of Trustees, appoint and reappoint an executive vice-president, who shall be the chief executive officer of the Medical Society of the State of New York, to manage and direct the activities of the State Society including disbursement of its funds when duly authorized. He shall be a member of all boards, commissions, and committees with voice but without vote. The executive vice-president shall appoint and reappoint a deputy executive vice-president subject to the approval of the Council.

The Council shall act on the applications for life membership which have been submitted by the component county medical societies. A majority vote of the Council present and voting shall be necessary for election to life membership.

The Council shall have responsibility for all publications of the Medical Society of the State of New York and their distribution. For the purpose of required announcements, the official publication of the State Society shall be the *New York State Journal of Medicine.*

Special committees shall report to the Council and shall be subject to the Council unless otherwise instructed by the House of Delegates.

The Council, with the aid of the general counsel of the Medical Society of the State of New York, shall examine the constitution and bylaws of component county medical societies and district branches and/or all amendments thereto which shall be submitted to the Council for approval and shall approve or disapprove of said amendments.

The duties of the Council shall include the supervision of all commissions, committees, and activities of the Medical Society of the State of New York.

The Council shall also keep constantly advised of the activities of and collaborate with the health and social service departments of the State and with hospitals, clinics, and social service agencies in furthering the health of the community.

Commissions and committees of the Council may include any member of the Medical Society of the State of New York who shall be appointed by the president subject to the approval of the Council.

The Council shall control all arrangements for the annual convention of the Medical Society of the State of New York.

SECTION 3. TRIALS FOR MALFEASANCE

The Council shall sit as a trial body for hearings on charges of malfeasance and/or nonfeasance.

Charges of malfeasance or nonfeasance preferred by a member against an officer, councilor, trustee, or member of a board, commission, or committee of the Medical Society of the State of New York shall be transmitted to the president in writing. The president shall order a trial on said charges by the Council, or a committee thereof.

Charges of malfeasance or nonfeasance preferred by a member against the president shall be transmitted in writing to the secretary of the Medical Society of the State of New York and shall be considered by the Council with the vice-president presiding.

The accused shall be given at least ten days' notice of such trial and of the charges against him and shall have full opportunity to defend himself, but no such officer, councilor, trustee, or member of a board, commission, or committee shall be removed or otherwise disciplined except by a three-fourths vote of the Council.

In case any such officer, councilor, trustee, or member of a board, commission, or committee shall be removed, he may appeal from the decision of the said Council to the House of Delegates; but, pending the determination of such appeal, he shall not exercise the functions of his office.

SECTION 4. EXECUTIVE COMMITTEE

The Council shall establish an executive committee to be composed of the president, the vice-president, the president-elect, the immediate past-president, the secretary, the treasurer, the chairman of the Board of Trustees, and two additional members of the Council appointed by the president with the approval of the Council.

This committee shall be appointed by the president and shall serve only during his tenure as president.

The executive committee shall have the authority to take action in case of emergency arising in the interim between the meetings of the Council to protect the interests and purposes of the Medical Society of the State of New York as set forth in these Bylaws. In times of such emergency, the executive committee shall have all the powers and duties which are conferred on the Council, and it shall at all times assist the Council. Any action taken by the executive committee shall be reported in full to the Council at its next meeting.

SECTION 5. MEETINGS

The newly elected Council shall meet at the close of the annual meeting of the House of Delegates. The Council and Executive Committee shall meet at regular intervals at times and places that shall be fixed by the president with the approval of the Council. Twenty-five percent of the members of the Council in writing may require the president to call a special meeting for such time and place as he shall designate, within ten days of his receipt of such notice.

The notices of the regular meetings of the Council shall state the date, place, hour, and shall be mailed postpaid to each member by first class mail not less than ten nor more than fifty days before a meeting.

The affidavit of mailing by the secretary of the Medical Society of the State of New York to the last recorded address of the Council member shall be deemed sufficient proof of the service on each and every Council member for any and all purposes.

Council members must receive at least three days' notice by letter or telegram from the State Society's office of a special meeting, which shall state the date, place, hour, and items of business that will be considered.

A quorum shall consist of 14 members of the Council.

The following shall be the order of business at meetings of the Council, which may be altered by the chairman with the consent of the Council:

1. Calling the meeting to order
2. Roll call
3. Reading of minutes
4. Communications
5. Report of the Executive Committee
6. Report of the president
7. Report of the secretary
8. Report of the treasurer
9. Report of the chairman of the Board of Trustees
10. Reports of councilors
11. Report of the executive vice-president
12. Reports of commissions and committees
13. Unfinished business
14. New business
15. Adjournment

ARTICLE V. OFFICERS

The officers of the Medical Society of the State of New York shall be a president, a president-elect, a vice-president, a secretary, an assistant secretary, a treasurer, an assistant treasurer, a speaker, and a vice-speaker of the House of Delegates. They shall take office at the termination of the annual meeting at which they are elected and shall serve for one year or until their successors have been duly chosen.

No person may serve, consecutively, more than five terms as secretary, treasurer, assistant secretary, assistant treasurer, speaker, or vice-speaker. An unexpired term shall not be construed as a term of office.

No salaried employee of the Medical Society of the State of New York shall be an elected officer of the Medical Society of the State of New York. For the purposes of this article an honorarium shall not be considered as a salary.

SECTION 1. VACANCIES AND SUCCESSION

An officer shall practice or maintain a residence or an office in the State of New York, otherwise his office in the Medical Society of the State of New York shall be declared vacant.

The president-elect shall succeed to the presidency at the end of his term as president-elect.

In the event of the president's death, resignation, removal, permanent incapacity, or refusal to act, the vice-president shall succeed him and shall serve for the remainder of the unexpired term.

If the president is temporarily incapacitated for service by injury, ill health of himself or his family, important professional duties, or any other mandatory absence, the vice-president shall become acting president for the duration of such incapacity of the president. The president shall promptly notify the vice-president of his incapacity and request his attention to the duties of the office and shall also promptly notify the vice-president of the end of the period of temporary incapacity before resuming the office of the presidency.

If the office of vice-president becomes vacant, for any reason whatsoever, the Council, when the House of Delegates is not in session, shall elect a successor for the unexpired term.

If the office of president-elect becomes vacant, it shall remain so until the next annual meeting of the House of Delegates, at which an eligible member shall be elected to become president. A president-elect to succeed him at the end of his term shall also be elected at the same meeting.

The assistant secretary, the assistant treasurer, and the vice-speaker shall serve as the secretary, the treasurer, and the speaker, respectively, whenever these senior officers are incapacitated for service by injury, ill health of themselves or families, important professional duties, or any other mandatory absences. This shall be construed so as to include duty at or during meetings of the Board of Trustees as well as the other official duties designated for the senior officer. The senior officer shall promptly notify the junior officer of his incapacity and request his attention to said duties. When the period of incapacity is ended, the senior officer shall promptly notify the junior officer of the end of the period of temporary incapacity before resuming office.

If the offices of secretary, treasurer, or speaker become vacant, for any reason whatsoever, these officers shall be succeeded by the assistant secretary, assistant treasurer, and vice-speaker, respectively, for the unexpired term.

If the office of assistant secretary, assistant treasurer, or vice-speaker becomes vacant, for any reason whatsoever, the Council, when the House of Delegates is not in session, shall elect a successor for the unexpired term.

If an elected officer is absent from three consecutive regular meetings of the Council, without proper excuse, the Council shall declare his office vacant. The vacancy shall be filled as provided in the Bylaws.

Any elected officer of the Medical Society of the State of New York who is called into active service in the armed forces of the United States or in the United States Public Health Service may, on application to the Council, be granted leave of absence for any portion of his term of office during which he is on active service. During such absence, his duties shall be delegated as the Council may direct except where such delegation is already provided for elsewhere in the Bylaws.

SECTION 2. DUTIES

President

The president shall set the dates and place of regular meetings of the Council and Executive Committee and shall preside at the meetings of the Medical Society of the State of New York, the Council, and the Executive Committee.

He shall name the appointive members of the Executive Committee and appoint the chairmen and members of all committees and the chairmen of all commissions of the Council with the approval of the Council. He shall appoint all other committees not otherwise provided for, with the approval of the Council.

Within three months after assuming the office of president, he shall appoint, as prescribed in Article XI, Section 2, a nominating committee, whose names he shall cause to be published in the official publication of Medical Society of the State of New York.

He shall be an *ex officio* member of all boards, commissions, and committees with voice and vote, with the exception of the Judicial Council, the Board of Trustees, and the Nominating Committee wherein he shall have voice but no vote.

With the approval of the Council, he shall apoint a member to the Judicial Council to succeed the member with an expiring term, and in the event of a vacancy occasioned otherwise, he shall appoint a member for the unexpired term.

He shall appoint, with the approval of the Council, representatives to other medical societies or similar bodies as the interests of the Medical Society of the State of New York may require.

He shall appoint a sufficient number of delegates or alternate delegates to the House of Delegates of the American Medical Association when the full quota of those elected is not available, as provided in the Bylaws, Article VIII, paragraphs 3 and 4.

He shall assign Councilors as liaison between the Council and specific county medical societies for the purpose of the dissemination of information to such societies.

He shall appoint, with the approval of the Council, a chairman and a secretary for each organized session of the Medical Society of the State of New York.

When charges by a member of malfeasance or nonfeasance are preferred against any other officer, councilor, trustee, or member of a board, commission, or committee of the Medical Society of the State of New York and are transmitted to the president in writing, he shall order a trial on said charges by the Council, or a committee thereof.

He shall assign the special branches of work for which the members of the Council shall be responsible, with the approval of the Council.

He shall make an annual report to the House of Delegates.

He shall deliver an address at the annual meeting of the House of Delegates. He shall perform such other duties as the House of Delegates or the Council shall require.

He shall attend all meetings of the House of Delegates of the American Medical Association.

President-Elect

The president-elect shall perform such duties as may be requested by the president.

The president-elect shall attend all meetings of the House of Delegates of the American Medical Association.

Vice-President

The vice-president shall perform the duties of the president in the latter's absence.

He shall preside over the Council when it is deliberating on charges of malfeasance or nonfeasance preferred against the president.

Secretary

The secretary shall attend all meetings of the Medical Society of the State of New York, the House of Delegates, the Council, the Board of Trustees, and the Judicial Council, and shall keep minutes of their respective proceedings. These minutes shall be copied from a stenographer's notes with such deletion only as will not modify, alter, or becloud the history of the actions of the said bodies. The stenographer's typewritten copy shall be preserved until ordered destroyed by the House of Delegates.

He shall perform such other duties as may be prescribed from time to time by the House of Delegates or the Council. He shall attend all meetings of the House of Delegates of the American Medical Association.

The secretary shall be the custodian of the seal of the Medical Society of the State of New York and of all books of records and papers belonging to the State Society, except such as properly belong to the treasurer, and shall keep an account of and promptly turn over to the treasurer all funds of the State Society which come into his hands.

He shall record the name and date of admission of each member of the Medical Society of the State of New York.

He shall provide for the registration of the members at all conventions of the Medical Society of the State of New York. With the aid and cooperation of the secretaries of the component county medical societies, he shall keep a proper register of all registered physicians of the State by counties.

He shall conduct the official correspondence, notifying members of meetings, officers, councilors, trustees, and board members of their election, and commissions and committees of their appointments and duties.

He shall affix the seal of the Medical Society of the State of New York to the credentials of delegates to the American Medical Association and to such other papers and documents as may require the same.

He shall make an annual report to the House of Delegates. Acting in cooperation with the Council, he shall prepare and issue all programs.

He shall be an *ex officio* member of all boards, commissions, and committees with voice and vote, with the exception of the Judicial Council, the Board of Trustees, and the Nominating Committee wherein he shall have voice but no vote.

Assistant Secretary

The assistant secretary shall aid the secretary in the work of his office.

Treasurer

The treasurer shall keep accurate books of accounts of all moneys of the Medical Society of the State of New York which he may receive and shall disburse or cause to be disbursed the same when duly authorized. He shall be the official custodian of all securities and the income thereof owned by the State Society, subject to the direction and disposition of the Board of Trustees. The Board of Trustees may select a bank or trust company to act as custodian in the place of the treasurer of all or any part of such securities and to act as agent of the State Society in collecting the income therefrom.

He shall collect, on or before the first day of April in each year, from the treasurer of each component county medical society, the Medical Society of the State of New York per capita annual dues. He shall collect any assessments voted by the House of Delegates or the Council. He shall, at the expense of the Medical Society of the State of New York, give a bond for the faithful performance of his duties, which shall be approved by the Board of Trustees as to amount, form, and surety. He shall make an annual report to the House of Delegates and report to the Council at each of its meetings. He shall be an *ex officio* member of the Professional Medical Liability Insurance and Defense Board, with voice but without vote.

Assistant Treasurer

The assistant treasurer shall aid the treasurer in the work of his office.

He shall, at the expense of the Medical Society of the State of New York, give a bond for the faithful performance of his duties, which shall be approved by the Board of Trustees as to the amount, form, and surety.

Speaker

The speaker shall preside at all meetings of the House of Delegates. He shall appoint all committees to serve during the meeting of the House of Delegates at least thirty days in advance of the meeting. All resolutions submitted by component county medical societies, district branches, scientific sections, and medical schools to be presented to the House of Delegates should be forwarded to the speaker at least forty-five days in advance of the annual meeting of the House and referred by him to the appropriate reference committees; and all resolutions sent in subsequent to forty-five days should be presented to the House and referred to the appropriate reference committees.

Vice-Speaker

The vice-speaker shall perform the duties of the speaker when so requested by the speaker.

ARTICLE VI. TRUSTEES

There shall be a Board of Trustees which shall have charge of all property including trust funds and shall supervise the financial affairs of the Medical Society of the State of New York.

SECTION 1. COMPOSITION

The Board of Trustees shall consist of seven members elected by the House of Delegates. The president, secretary, treasurer, executive vice-president, deputy executive vice-president, and general counsel shall sit with the Board of Trustees with voice but without vote.

One trustee shall be elected annually for a term of five years, but whenever the terms of two trustees expire in the same year, two trustees shall be elected each for five years.

To be eligible for election as trustee, a member shall have served at least two years as an officer or at least three years as a councilor, or at least five years as a member of the House of Delegates.

No person shall serve more than one term as a trustee. An unexpired term shall not be construed as a term of office.

A trustee shall practice or maintain a residence or an office in the State of New York, otherwise his position in the Medical Society of the State of New York shall be declared vacant.

If a trustee is absent from three consecutive regular meetings of the Board, without proper excuse, the Council shall declare his position vacant and elect a successor for the unexpired term.

In the event of a vacancy, a trustee shall be elected by the Council to serve until the next meeting of the House of Delegates at which time the House of Delegates shall elect a trustee to fill the unexpired term.

SECTION 2. DUTIES

The annual budget estimate, prepared by the Committee on Budget and Finance, after its approval by the Council, shall be submitted to the Board of Trustees for its approval.

All resolutions or recommendations of the House of Delegates or Council pertaining to expenditures of money must be approved by the Board of Trustees before the same shall become effective.

Should the Board of Trustees disapprove of the expenditure of any funds voted for by the House of Delegates or the Council, then and in that event, the Board of Trustees shall return the matter to either the House of Delegates or the Council, if the House of Delegates is not in session, which may override such disapproval by a three-quarter vote and direct the expenditure of such funds. The Board of Trustees shall not vote on this issue at a meeting of the House of Delegates and the chairman of the Board of Trustees shall not vote on this issue at the Council.

The Board of Trustees shall make and execute all contracts for the Medical Society of the State of New York. The fiscal year shall begin January 1 and end December 31 of each calendar year.

All moneys of the Medical Society of the State of New York received by the Board of Trustees, Council, or any member or agent thereof, shall be paid to the treasurer of the State Society. The Board of Trustees shall approve the bond of the treasurer and the assistant treasurer as to amount, form, and surety, and shall employ a certified public accountant licensed by the State of New York to audit the accounts of the treasurer and secretary and other agents of the State Society and present a statement of the same in its annual report to the House of Delegates.

The chairman of the Board of Trustees shall make a report to the House of Delegates of its transactions for the year and of the amount of money belonging to the Medical Society of the State of New York under its control.

SECTION 3. MEETINGS

The Board of Trustees shall meet immediately at the close of the annual meeting of the House of Delegates, and shall organize under the temporary chairmanship of the member senior in service on the Board, elect a permanent chairman, and fix the time and place of its regular meetings. Should two trustees have similar seniority, choice between them for temporary chairmanship shall be by lot.

The Board of Trustees shall meet at least bimonthly, except in July and August.

The notices of the regular and special meetings of the Board of Trustees shall state the date, place, and hour and shall be mailed first class postpaid to each member not less than ten nor more than fifty days before a regular meeting and at least five days before a special meeting.

The affidavit of mailing by the secretary of the Medical Society of the State of New York to the last recorded address of the trustee shall be deemed sufficient proof of the service on each and every trustee for any and all purposes.

Any three members of the Board of Trustees may require the chairman to call a special meeting at the office of the Medical Society of the State of New York for such time as shall be designated by them in writing.

A quorum shall consist of four members of the Board of Trustees.

The following shall be the order of business at the meetings of the Board of Trustees, which may be altered by the chairman with the approval of the Board:

1. Calling the meeting to order
2. Roll call by the secretary
3. Reading of minutes
4. Communications
5. Reports
6. Unfinished business
7. New business
8. Adjournment

ARTICLE VII. JUDICIAL COUNCIL

There shall be a Judicial Council which shall have jurisdiction to hear and determine all appeals from decisions on discipline of component county medical societies or decisions of such societies which may involve the privileges, rights, or standing of members, whether in relation to one another or to component county medical societies or to the Medical Society of the State of New York.

It shall hear also from applicants on appeals from the action of a component county medical society in excluding them from membership.

SECTION 1. COMPOSITION

The Judicial Council shall consist of five appointed members. One member shall be appointed by the president each year for a term of five years with the approval of the Council.

No member shall serve for more than two consecutive terms, but a member appointed to serve an unexpired term shall not be regarded as having served a term unless he has served three or more years.

A member of the Judicial Council shall practice or maintain a residence or an office in the State of New York, otherwise his position on the Judicial Council shall be declared vacant.

In the event of a vacancy, a member shall be appointed by the president for the unexpired term with the approval of the Council.

The president and secretary of the Medical Society of the State of New York shall be *ex officio* members of the Judicial Council with voice but no vote. The executive vice-president, the deputy executive vice-president, and the general counsel of the Medical Society of the State of New York shall sit with the Judicial Council with voice but without vote.

SECTION 2. DUTIES AND PROCEDURES

A member of a component county medical society who shall have been disciplined or directed to suffer discipline in any degree by any final decision of his component county medical society and who shall have exhausted his right of appeal, if any, with a component county medical society, feeling aggrieved by the decision of such society, may appeal to the Judicial Council of the Medical Society of the State of New York from the decision of such component county medical society by filing a notice of appeal with the secretary of the State Society and with the secretary of such component county medical society within three months after such final decision by such component county medical society.

An applicant for membership in a component county medical society who has been excluded from membership in such society may likewise appeal from the action of said society.

The Judicial Council shall investigate also all charges preferred (a) by a member of a component county medical society against a component county medical society of which he is not a member; and (b) by a component county medical society against another such component county medical society or a member thereof.

A notice of appeal shall set forth in writing the name of the appellant, the name of such component county medical society and the date and substance of the decision appealed from, and shall indicate the ground or grounds upon which such appeal is taken. If the appellant desires to be present, with or without counsel, at the hearing of said appeal, the notice of appeal must so state. In that event, the appellant must file with the notice of appeal a bond in the sum of $500 to cover the costs of said appeal. If the appellant fails to appear in person or be represented by counsel on hearing of said appeal, he shall forfeit to the Medical Society of the State of New York such shares of said bond as represents necessary expenditures incident to convening the Judicial Council for the hearing of said appeal.

On filing a notice of appeal, the appellant and the component county medical society shall submit to the secretary of the Judicial Council all records, minutes, letters, papers, and all written evidence, including a digest of all testimony not stenographically reported relating to the matter. All data so submitted shall be available only to the Judicial Council.

The Judicial Council shall consider the appeal on the data so submitted to it and may affirm, modify, or reverse the decisions so appealed from by a majority vote of the members present and voting. If, in its opinion, the taking of further evidence is advisable, the Judicial Council may summon witnesses and proceed to take such evidence in such manner as it may deem proper and render its decision by a majority vote of those present and voting, which decision shall be final and binding. A member shall have the right of appeal to the Judicial Council of the American Medical Association.

Whenever the Judicial Council has met, the secretary shall report the proceedings to the Council of the Medical Society of the State of New York at its next regular meeting.

The chairman shall submit an annual report of the Judicial Council to the House of Delegates.

SECTION 3. MEETINGS

Immediately at the close of the annual meeting of the House of Delegates the Judicial Council shall organize and elect its own chairman.

The secretary of the Medical Society of the State of New York shall be the secretary of the Judicial Council.

The Judicial Council shall meet on the call of the chairman. The notices of the meetings of the Judicial Council shall state the date, place, and hour and shall be mailed postpaid to each member not less than ten nor more than fifty days before a meeting.

The affidavit of mailing of the secretary of the Medical Society of the State of New York to the last recorded address of the member of the Judicial Council shall be deemed sufficient proof of the service on each and every member for any and all purposes.

A quorum shall consist of three members of the Judicial Council.

ARTICLE VIII. ELECTIONS

As the first business of the last scheduled session of the annual meeting of the House of Delegates, the officers, councilors, and trustees of the Medical Society of the State of New York, and the delegates to the American Medical Association shall be nominated and elected.

A member of the Medical Society of the State of New York who is in arrears for component county medical society dues or State Society dues or assessments shall not be eligible for nomination to any office, the Council, the Board of Trustees, or as a delegate to the American Medical Association, or entitled to vote for any officer, councilor, trustee, or delegate.

The delegates to the American Medical Association shall be elected in the calendar year preceding the meeting of the House of Delegates of the American Medical Association to which they are elected. One half of the allotted number of delegates and alternate delegates shall be elected each year.

Nominations for delegate to the American Medical Association shall be made for not less than double the full number of delegates to be elected.

SECTION 1. BALLOTING

After the appointment of a sufficient number of tellers by the speaker and after all nominations have been made, the secretary of the Medical Society of the State of New York shall cause to be displayed in full sight of the House of Delegates a list of nominees for each office of the Medical Society of the State of New York and for delegates to the American Medical Association, arranged in alphabetical order, and shall also cause to be distributed a sufficient number of blank ballots for the use of the House of Delegates. These ballots shall have printed or stamped thereon the appropriate headings for each office with spaces thereunder in which may be written the name of the candidate or candidates to be voted for.

All elections for offices of the State Society and delegates to the American Medical Association shall be by ballot, each member of the House of Delegates depositing his ballot on roll call individually. When after the call for nominations from the floor, there is only one candidate for an office, the speaker shall direct the secretary to cast one ballot on behalf of the delegates. If there are more than two nominees for an office, with the exception of that of delegate to the American Medical Association, and none receives a majority of votes on the first ballot, the nominee receiving the lowest number of votes shall be dropped and a new ballot taken for that office. This procedure shall be continued until one of the nominees receives a majority of the votes cast when he shall be declared elected.

For the election of delegates to the American Medical Association, the delegates shall be declared elected in the order of the highest number of votes cast until the allotted number shall have been chosen; a corresponding number in the next highest order of votes cast shall be declared alternate delegates.

When the full quota of elected delegates or alternate delegates is not available for attendance at the meeting of the House of Delegates of the American Medical Association, the president of the Medical Society of the State of New York shall appoint and certify a sufficient number to complete the quota.

A duly elected delegate to the American Medical Association who does not serve as such because of reduction in number of delegates to which the Medical Society of the State of New York is entitled shall fill any vacancy which may occur in the delegation before alternate delegates are designated for that purpose.

The delegates and alternate delegates shall take office at the beginning of the calendar year following their election and shall serve for a term of two years.

ARTICLE IX. REFERENDUM

At any meeting of the House of Delegates two thirds of the members present and voting may order a referendum vote of the Medical Society of the State of New York on any question consistent with the Bylaws and in accordance with such regulations respecting the submission of the question as the House of Delegates may prescribe.

The members of the Medical Society of the State of New York shall vote thereon by mail. The polls shall be closed at the expiration of fifteen days after the mailing of the question; and if the members voting shall comprise a majority of all the active and life members of the Medical Society of the State of New York, a majority of such vote shall determine the question and be binding on the State Society and the House of Delegates.

When the House of Delegates is not in session the Council may in a similar manner order such a referendum by a two-thirds vote.

ARTICLE X. COMMITTEES OF THE HOUSE OF DELEGATES

SECTION 1. REFERENCE COMMITTEES

At least one month before the meeting of the House of Delegates the speaker shall appoint and publish in the official publication of the Medical Society of the State of New York such reference committees as he shall deem expedient for the purposes of the meeting. Immediately after the organization of the House of Delegates he shall formally announce the appointments of the committees. Only members of the House of Delegates shall be eligible for appointment to the reference committees. Such committees shall each consist of five members, three members constituting a quorum, and shall serve during the meeting of the House of Delegates for which they are appointed.

Annual reports of officers, Council commissions and committees, Board of Trustees, Judicial Council, district branches, and special committees shall be printed at least one month before the meeting of the House of Delegates and sent to the members of the reference committees appointed according to paragraph 1, for their preliminary consideration.

All recommendations, resolutions, measures, and propositions presented to the House of Delegates and which have been duly seconded shall be referred by the speaker to the appropriate reference committees, except that reports of committees of the House of Delegates may, at the discretion of the House, be presented directly to the House without referral to the reference committees.

Each reference committee shall consider such business as may have been referred to it and shall report promptly to the House.

Any member of the Medical Society of the State of New York in good standing shall have the right to appear before any reference committee and participate in its deliberations.

SECTION 2. COMMITTEE ON BYLAWS

The House Committee on Bylaws shall be appointed annually by the speaker. It shall consist of at least five members including a chairman, all of whom shall be members of the House. The president, secretary, and the speaker shall be *ex officio* members with voice and vote. The executive vice-president, deputy executive vice-president, and general counsel of the Medical Society of the State of New York shall be members of the committee with voice but without vote.

It shall be the duty of the committee to study all proposed amendments to the *Bylaws* and the *Principles of Professional Conduct* of the State Society and to report thereon at the annual meeting of the House of Delegates following the meeting at which such amendments are proposed. The committee shall include in its report recommendations for action on the proposed amendments with reasons for such recommendations.

It shall be the duty of the committee to suggest amendments to or revisions of the *Bylaws* and the *Principles of Professional Conduct* of the Medical Society of the State of New York.

The report of the House Committee on Bylaws shall be presented directly to the House, without referral to a reference committee.

SECTION 3. SPECIAL COMMITTEES

Special committees may be created by the House of Delegates to perform the special functions for which they are created. They shall be appointed by the speaker or other officer presiding pro tempore over the meeting at which the committee is authorized.

ARTICLE XI. COUNCIL COMMISSIONS AND COMMITTEES

SECTION 1. ORGANIZATION

Committees of the Council are grouped by the related nature of their purposes and functions. A commission is composed of the chairmen of all committees within such a group.

Subject to the approval of the Council, the president shall appoint the chairmen and members of all of its committees and the chairmen of the commissions.

Any member of the Medical Society of the State of New York is eligible for membership on committees and commissions of the Council.

All chairmen of such commissions and committees shall have the right to present their reports in person to the Council and to engage in the discussion of such reports. Members of such commissions and committees shall have the privilege of presenting minority reports, and both the majority and minority reports shall be published.

Any *ex officio* member of a committee who enjoys that status by being a duly elected officer of the Medical Society of the State of New York shall have all the rights, responsibilities, and duties of any other member of the committee.

SECTION 2. NOMINATING COMMITTEE

The Nominating Committee shall be appointed by the president from a list of not less than three or more than five names submitted by the respective district branches, in conformity with Article V, Section 2, paragraph 3. It shall consist of 11 members, 1 from each district branch and 2 members at large.

In the event that a member of the Nominating Committee who has been selected as the representative of a particular district branch (or his alternate) shall be unable to attend the meeting of this committee, the president shall appoint an at large member, from the district branch whose representative is absent, to represent the interests of that district on the Nominating Committee. It shall be the duty of this committee to propose and nominate members of the Medical Society of the State of New York for all vacancies to be filled at the ensuing annual meeting of the House of Delegates. These recommendations shall be made to the House of Delegates in the same manner as prescribed in Article X, Section 1, paragraph 2.

SECTION 3. PROFESSIONAL MEDICAL LIABILITY INSURANCE AND DEFENSE BOARD

A committee to be known as the Professional Medical Liability Insurance and Defense Board shall be appointed by the president with the approval of the Council. It shall consist of nine members including a chairman, each appointed for a three-year term. No member shall serve for more than two consecutive terms. A vacancy created by expiration of a term shall be filled by the president, with the approval of the Council, by appointment of a member for three years. Other vacancies shall be filled for the unexpired term in similar manner. The secretary shall be an *ex officio* member of the committee with voice and vote. The treasurer shall be an *ex officio* member of the committee with voice but without vote. The general counsel and indemnity representative shall attend all meetings with voice but without vote. It shall be the duty of the committee to study and supervise, on behalf of the Medical Society of the State of New York, all matters having to do with professional medical liability insurance and defense.

ARTICLE XII. SPECIALTY SOCIETY REPRESENTATION

The House of Delegates shall designate those specialty societies entitled to representation in the Medical Society of the State of New York. Such specialty societies shall correspond to the Statewide specialty societies recognized by the Council of the Medical Society of the State of New York.

Each of the Statewide specialty societies recognized by the Council of the Medical Society of the State of New York shall be requested to submit to the office of the Executive Vice-President the name of one delegate and one alternate delegate not less than ninety days prior to the annual meeting of the House of Delegates. All such designated delegates must be members of the Medical Society of the State of New York.

Should the delegate or alternate of a specialty society be unable to serve in the House of Delegates, the president of the specialty society shall designate a substitute delegate and shall so notify the secretary of the Medical Society of the State of New York in writing.

The Scientific Program Committee shall be responsible for planning and presenting the program at the Annual Continuing Medical Education Assembly which shall be held at a time and place designated by the Council. The committee shall be composed of a chairman and associate chairmen and one MSSNY member from each specialty society that has been recognized by the Council, as provided in Article XII, paragraph 1 of the Bylaws, to be selected from a list of one or more physicians recommended by the above-mentioned specialty societies. The committee shall be appointed annually by the President of the Medical Society of the State of New York, with the approval of the Council.

ARTICLE XII-A. HOSPITAL MEDICAL STAFF SECTION

The hospital medical staff section is authorized to be represented in the House of Delegates by (1) delegate. The hospital medical staff section shall represent physicians on the medical staffs of acute care hospitals located in New York State.

The method of electing the delegate representing the hospital medical staff section shall be determined by the Council.

ARTICLE XIII. MEETINGS

SECTION 1. ANNUAL MEETING OF THE HOUSE OF DELEGATES

There shall be an annual meeting of the Medical Society of the State of New York to be held at a time and place designated by the House of Delegates or by the Council.

SECTION 2. ANNUAL MEETING OF MEDICAL SOCIETY OF THE STATE OF NEW YORK

The Medical Society of the State of New York shall hold its annual meeting at the last scheduled session of the House of Delegates, while the House is recessed following the annual elections. The president shall preside at this annual meeting of the State Society, which shall include the induction of the incoming president. The incoming president shall deliver his inaugural address at the annual meeting of the State Society.

Following the adjournment of the annual meeting, the House of Delegates shall reconvene to complete its agenda and receive the report of the tellers.

SECTION 3. SPECIAL MEETINGS

Special meetings of the Medical Society of the State of New York shall be called by the president on the request in writing of members entitled to cast ten percent of the total number of votes entitled to be cast at such meeting. Such request must specify the date and month of such meeting, which shall not be less than two nor more than three months from the date of such written demand. The president of the Society upon receiving the written request shall direct the secretary to promptly give notice of such meeting. If the secretary shall fail to give such notice within five business days of such request, any member signing such request may give the required notice.

SECTION 4. ORGANIZATION AND PROCEDURES

The notices of the annual meeting of the House of Delegates and annual and special meetings of the Medical Society of the State of New York shall state the date, place, and hour and shall be mailed postpaid to each member by first class mail not less than ten nor more than fifty days before a meeting.

Publication of such notice in the official publication of the Medical Society of the State of New York shall be considered as complying with this provision.

The affidavit of mailing by the secretary of the Medical Society of the State of New York to the last recorded address of the member shall be deemed sufficient proof of the service upon each and every member for any and all purposes.

Each member in attendance at the annual meetings of the Medical Society of the State of New York shall enter his name and the name of the component county medical society to which he belongs in a register to be kept by the secretary of the State Society for that purpose. No member shall take part in any of the proceedings of such convention until he shall have complied herewith.

All members in good standing so registered may attend and participate in the proceedings and discussions of the Annual Continuing Medical Education Assembly of the Medical Society of the State of New York.

No address or paper before the Medical Society of the State of New York, except those of the president and president-elect, shall occupy more than twenty minutes in its delivery.

All papers read before the Medical Society of the State of New York at its Annual Continuing Medical Education Assembly shall become the property of the State Society. Whenever such paper shall be deemed not acceptable for publication in the *New York State Journal of Medicine* it shall be returned to the author as promptly as possible after its receipt in the publication office of the State Society.

The following shall be the order of business at the annual meeting of the Medical Society of the State of New York:

1. Calling the State Society to order
2. Reading of minutes of the last meeting by title
3. Induction of incoming president
4. Inaugural address by incoming president
5. Adjournment

The rules contained in *Sturgis Standard Code of Parliamentary Procedure* shall govern the Medical Society of the State of New York in all cases in which they are not inconsistent or in conflict with the Bylaws of the State Society.

ARTICLE XIV. FUNDS

Funds shall be raised by annual dues levied on each active member at a uniform per capita rate throughout the State. Funds may also be raised in any other manner approved by the House of Delegates or by the Council when the said House of Delegates shall not be in session.

The approval of the Council and of the Board of Trustees shall be necessary for the expenditure of any funds of the Medical Society of the State of New York, except that the said Board may delegate, to such person or persons as it sees fit, the authority to expend funds of the State Society in amounts and under conditions to be determined by said Board, on recommendation of the Council.

ARTICLE XV. DUES

The annual dues shall be determined by the House of Delegates.

Assessments can be levied by the House of Delegates or the Council and shall be payable within a period of time specified by them.

The dues and assessments of those active members who have been graduated from medical or osteopathic college not more than five calendar years, not counting active service in the armed forces of the United States or in the United States Public Health Service, shall be one third the amount levied on all other active members. The dues and assessments of those active members who have not completed their continuous residency training shall be one tenth the amount levied on all other active members. In no case may an active physician continue to pay such reduced dues more than seven years after the date of graduation from medical or osteopathic school. The dues and assessments of those active members entering solo practice for the first time, who are not otherwise eligible for reduced dues as set forth in prior provisions in this paragraph, shall be one half the amount levied on all other active members, for the first two years of solo practice; full dues shall be paid after the first two years of solo practice. Once an active member pays full dues, he shall no longer qualify for half-dues status.

Life and honorary members shall not be required to pay dues or assessments to the Medical Society of the State of New York.

Annual dues are due and payable on the first day of January each year. The dues year shall coincide with the calendar year, January 1 to December 31.

Any member, except a member who is eligible for and has applied for life membership, whose component county medical society and State Society dues are unpaid after April 1 of any current year or whose assessments are unpaid by the specified time is not in good standing and shall be deemed to be in arrears.

A member whose dues are unpaid after May 1 of any current year or whose assessments are unpaid one month after the specified date shall be dropped from the roles of membership of his component county medical society and the Medical Society of the State of New York upon reasonable notice to such member by his component county medical society or the State Society, and without further action on the part of either the component county medical society or the State Society, and on such date he shall automatically cease to be a member of the component county medical society and State Society. In the case of nonpayment of dues, the reasonable notice to be provided shall commence on April 1, or as soon as possible thereafter, upon the determination that such member is in arrears.

Dues and State Society assessments of a member elected or reinstated after October 1 shall be credited to the succeeding year, but no member dropped for nonpayment of dues and assessments shall be reinstated until he has, in addition, paid his dues and assessments for the year in which he was dropped.

The dues of an active or student member of the State Society may be remitted for the current year by action by the Council on account of illness, financial hardship, or temporary active service in the armed forces of the United States or in the United States Public Health Service, when the request for such remission is made by the member's component county medical society, except in the case of student members who shall make application for remission directly to the secretary. Such a request shall be accompanied by a brief summary of the reasons therefor. Remission of dues due to illness or financial hardship shall be reviewed annually.

ARTICLE XVI. EXPENSES

Allowances for expenses incurred in the actual performance of official duties by officers, councilors, trustees, members of the Judicial Council and of commissions and committees, delegates to the American Medical Association, and employees of the Medical Society of the State of New York shall be made in conformity with the following conditions.

The president and the president-elect shall be allowed a per diem and expenses when engaged on official business. The amount of the per diem shall be set by the House of Delegates.

All other officers, councilors, trustees, members of the Judicial Council, delegates to the House of Delegates of the American Medical Association or an alternate delegate who, at the direction of the Council, attends a meeting of the House of Delegates of the American Medical Association, members of commissions and committees of the Council, and of all special committees, members of the Medical Society of the State of New York appointed by the president or the Council to carry out special assignments for the State Society, and employees of the State Society shall be allowed traveling expenses when engaged on official business.

Members for life of the House of Delegates, delegates of the district branches, and student members, sitting in the House of Delegates, shall be allowed necessary expenses by the Medical Society of the State of New York.

Proper vouchers must be filed with the secretary of the Medical Society of the State of New York before any of the above allowances shall be made.

There shall be no allowances for the expenses, traveling or otherwise, for members of any reference committee.

Each district branch shall be entitled to receive a sum in accordance with the number of members in the district branch. The maximum allowable amount shall be $1,000 to district branches of less than 1,000 members; $2,000 to district branches of more than 999 but less than 2,000 members; $3,000 to district branches of more than 1999 but less than 4,000 members; $5,000 to district branches of more than 3999 members, exclusive of the work done by the Medical Society of the State of New York regarding notices, programs, and so on, to defray the expenses of such district branch, provided a proper statement of such expenses shall have been presented to the secretary.

All bills, claims, or vouchers herein provided for shall be filed within thirty days after the date of the incurring of such expense. This time may be extended for any cause by the Board of Trustees.

ARTICLE XVII. DISTRICT BRANCHES

SECTION 1. DIVISION

The membership of the Medical Society of the State of New York shall be divided into nine district branches, as follows:

The First District Branch shall comprise the members of the Medical Societies of the Counties of Bronx, Kings, New York, Queens, and Richmond.

The Second District Branch shall comprise the members of the Medical Societies of the Counties of Nassau and Suffolk.

The Third District Branch shall comprise the members of the Medical Societies of the Counties of Albany, Columbia, Greene, Rensselaer, Schoharie, Sullivan, and Ulster.

The Fourth District Branch shall comprise the members of the Medical Societies of the Counties of Clinton, Essex, Franklin, Fulton, Hamilton, Montgomery, Saratoga, Schenectady, Warren, and Washington.

The Fifth District Branch shall comprise the members of the Medical Societies of the Counties of Cayuga, Chenango, Herkimer, Jefferson, Lewis, Madison, Oneida, Onondaga, Oswego, and St. Lawrence.

The Sixth District Branch shall comprise the members of the Medical Societies of the Counties of Broome, Chemung, Cortland, Delaware, Otsego, Schuyler, Tioga, and Tompkins.

The Seventh District Branch shall comprise the members of the Medical Societies of the Counties of Livingston, Monroe, Ontario, Seneca, Steuben, Wayne, and Yates.

The Eighth District Branch shall comprise the members of the Medical Societies of the Counties of Allegany, Cattaraugus, Chautauqua, Erie, Genesee, Niagara, Orleans, and Wyoming.

The Ninth District Branch shall comprise the members of the Medical Societies of the Counties of Dutchess, Orange, Putnam, Rockland, and Westchester.

Changes in the number or membership of these district branches may be made by a two-third vote of the House of Delegates at any annual meeting thereof.

SECTION 2. AIMS AND ORGANIZATION

The objectives of the district branches shall be to promote the scientific, social, cultural, and other interests of the medical profession within the district and to cooperate with the Council of the Medical Society of the State of New York in any way which that body may advise.

Each district branch may adopt a constitution and bylaws for its government and may amend them. The constitution, bylaws, and amendments shall not be in conflict with the Bylaws of the State Society and before becoming effective they shall be approved by the Council.

SECTION 3. OFFICERS AND ELECTIONS

Each district branch shall elect a president for two years and a delegate to the House of Delegates for two years, but with the approval of the Council a district branch may elect a president for one year.

Each district branch shall elect such other officers as are provided for in its bylaws. They shall attend the business meetings of the branch.

In the case of the inability of the delegate of a district to serve, the vice-president shall serve as delegate, and if the vice-president is unable so to function, the president shall designate a substitute delegate to serve and shall so notify in writing the secretary of the Medical Society of the State of New York.

Any elected officer of a district branch who is called into active service in the armed forces of the United States or the United States Public Health Service may, on application to the Council, be granted leave of absence for any portion of his term of office during which he is on active service. During such absence his duties shall be designated as the Council may direct, except where such delegation is already provided for elsewhere in the Bylaws.

The president of each district branch shall visit the component county medical societies of the district at least once during his tenure of office and make a careful inquiry of the condition of the profession in each county in his district and shall report thereon to the House of Delegates.

ARTICLE XVIII. COMPONENT COUNTY MEDICAL SOCIETIES

SECTION 1. DEFINITION

The term "component county medical society" shall include all county medical societies now in affiliation with the Medical Society of the State of New York or which may hereafter be organized and chartered by the House of Delegates. There shall be but one component county medical society in each county affiliated with the State Society. If there should be an insufficient number of physicians in any of the counties of this State to form themselves into a component county medical society, such physicians may become members of the component county medical society of an adjoining county when eligible by the constitution and bylaws of such component county medical society.

SECTION 2. MEMBERSHIP

Eligibility for membership in a component county medical society shall be determined by that society. Except by the approval of the Council no physician shall be an active member in a component county medical society other than that of the county in which he practices or maintains legal residence.

Whenever an active member in good standing or a life member in any component county medical society removes to another county in this State, his name on his request shall be transferred to the roster of the component county medical society of the county to which he removes, without cost to him, provided that he files a certificate with the secretary of the Medical Society of the State of New York, signed by the president and secretary of the component county medical society from which he removes as to his good standing in such society, and provided his application for membership has been acted on favorably by the members of the component county medical society of the county to which he has removed.

No physician shall be granted membership by any county medical society in any category of membership which has been created for the benefit of physicians who neither reside nor practice in such county, unless and until such county medical society verifies, with the Medical Society of the State of New York, the fact that the applicant currently holds either active, junior, or life membership in another county of this State. This requirement applies with equal force whether the category of membership on the local county medical society level be designated "associate membership," "affiliate membership," "corresponding membership," "nonresident membership," or by any similar designation.

No member shall be an active member of more than one component county medical society, nor shall any component county medical society accept as a member a physician who does not practice or have a residence in that county in any other way than in accordance with the law governing transfers.

Every component county medical society shall provide for membership for graduates of recognized medical or osteopathic schools who are in continuous residency training. The constitution and/or bylaws of the component county medical society shall provide that residents shall be eligible for membership whether or not they are duly licensed and registered to practice in the State of New York. The resident members will have all the rights and privileges of active membership. Dues and assessments for the members in continuous residency training shall be no more than one tenth the amount levied on all other active members.

Except by the approval of the Council, no resident may be a member in a component county medical society other than that of the county where he is in residency training or where he maintains his legal residence.

SECTION 3. DUTIES OF OFFICERS

The secretary of each component county medical society shall keep a roster of its members in which shall appear the full name of each of said physicians, the date of his admission to such society, his residence, and the date when his license to practice medicine in this State was granted. He shall note any changes in said roster by reason of removal, death, or change of name, revocation of license, or other disqualification.

He shall forward said roster and information together with the names and places of residence of each of the officers of said society and the names and residences of each delegate to the House of Delegates from said society to the secretary of the Medical Society of the State of New York at least ninety days before the date of the annual meeting of said House of Delegates.

The treasurer of each component county medical society shall forward to the treasurer of the Medical Society of the State of New York the amount of the State Society per capita dues and/or assessments and the amount of all American Medical Association dues collected from members of his component county medical society as promptly as possible, but in any event before the first day of April of each year.

SECTION 4. MEETINGS

Each component county medical society shall hold an annual meeting for the purpose of electing officers and a delegate or delegates to represent it in the House of Delegates of the Medical Society of the State of New York in accordance with the Bylaws.

The annual meeting of each component county medical society shall be held between January 1 and July 1 of each year at a time which it shall determine.

All officers of the component county medical society shall enter on their official duties between May 1 and July 1 at a date determined by the component county medical society and shall serve for a term of one year or until their successors shall have been duly elected and qualified.

SECTION 5. RESIGNATIONS

An active or life member in good standing whose resignation from membership in his component county medical society shall have been duly accepted, shall be considered to have resigned from the Medical Society of the State of New York.

When a member in good standing, other than a life or honorary member, ceases, between May 1 and December 31 of any year, to reside and practice in the State of New York, he shall be considered to have resigned from membership effective as of that December 31. If such cessation to reside and practice occurs between January 1 and May 1 of any year, he shall, provided he has been in good standing for the prior calendar year, be considered to have resigned from membership effective as of the previous December 31.

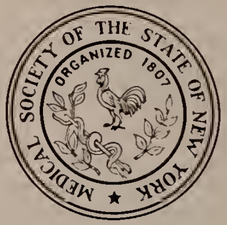
On resignation, a member shall forfeit all rights and title to any share in the privileges and property of the Medical Society of the State of New York, the district branch, and his component county medical society.

SECTION 6. CONSTITUTION AND BYLAWS

Each component county medical society shall adopt a constitution and/or bylaws for regulation of its affairs and may amend them. The constitution, bylaws, and amendments shall not be in conflict with the Bylaws of the Medical Society of the State of New York, and before becoming effective, they shall be approved by the Council.

ARTICLE XIX. SEAL OF THE MEDICAL SOCIETY OF THE STATE OF NEW YORK

The seal of the Medical Society of the State of New York shall be as follows:



ARTICLE XX. AMENDMENTS

Amendments to the *Bylaws* or to the *Principles of Professional Conduct*, except such as are obligatory by law, shall be made only at an annual meeting of the House of Delegates after having been submitted in writing at a previous annual meeting and having been published in the official publication of the Medical Society of the State of New York at least once and at least one month before the annual meeting at which action shall be taken.

The affirmative vote of two thirds of the House of Delegates present and voting shall be necessary for adoption of any amendment.

Amendments made necessary by law shall be made either by the Council or House of Delegates whenever such necessity exists.

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NOTES

MEDICAL SOCIETY OF THE STATE OF NEW YORK
ORGANIZED 1807

Classified Advertising

New York State Journal of Medicine

GENERAL INFORMATION

All classified advertisements are payable in advance, except for government agencies and advertising agencies; a 15% commission to recognized advertising agencies.

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Closing date: 30 days before mailing date

Circulation: 27,000 (mainly physicians & medical libraries)

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TAKE CARE OF YOUR LUNGS. THEY'RE ONLY HUMAN.

Listen, this is important. You see your insides down there? Sure, your heart and your brain and all that stuff is there. But look at your lungs! I mean they are important! Without your lungs, nothing works! So don't smoke. Because smoking, oh, it's terrible! Your lungs get darker and get damaged. Smoking makes your lungs work harder and harder until, whew! You can't breathe at all! So don't smoke. That's all.

Sid Caesar

AMERICAN LUNG ASSOCIATION®
The Christmas Seal People®

PHYSICIANS WANTED—CONT'D

GENERAL INTERNIST—FAMILY PHYSICIAN: Associate wanted leading to partnership to replace retiring partner. Private middle-class internal medicine and family medicine practice, south shore Nassau County. Contact: Howard Grill, M.D., 121 South Ocean Ave., Freeport, N.Y. 11520. (516) 379-5005.

PHYSICIANS, EMERGENCY MEDICINE, full-time and/or part-time to begin work immediately in progressive moderate volume E.D. Prefer board certification in EM, IM, FP or Surgery. Certified ACLS and/or ATS highly desirable. Flexible scheduling and independent contractor status. Excellent compensation. Send letter of interest and CV to Nancy Champion, Director of Human Resources, St. Lukes Memorial Hospital Center, P.O. Box 479, Utica, NY 13503.

GENERAL SURGEON NEEDED. Multispecialty group. Excellent opportunity for qualified individual. Contact: Dr. Robert Caplan, 1925 Mountain View, Longmont, Colo. 80501. 1 (303) 776-1234.

DIRECTOR—EMERGENCY DEPARTMENT: Eastern Upstate New York, a 296-bed facility with 37,000 annual ED visits seeks an emergency physician capable of assuming directorship of department with six full-time physicians. Current director stepping down. Competitive salary and benefits including malpractice. Twelve-hour shifts with double coverage during peak hours. Prefer ABEM certified/prepared, with EM, ABFP or ABIM residency plus full-time experience. Reply Dept. 326, c/o NYSJM.

ORTHOPEDIC SURGEONS, NEUROSURGEONS needed full or part time for a group of modern highly professional private evaluation centers currently located in Buffalo, Rochester and Syracuse, expanding rapidly. Bankers hours, excellent remuneration, no hassles. Write, including C.V., H. Lewis, M.D., 444 East Genesee, Syracuse, NY 13202 or call (315) 472-2500.

EMERGENCY PHYSICIAN for Oswego, New York. City population 25,000 on Lake Ontario one hour from Syracuse. 1700 patients per month with moderate amount of trauma. Fee-for-service as independent subcontractor. Malpractice provided, CME stipend, potential for distribution after 2 years. 42 hour work week. (15 shifts per month). Please call Ken Baker, Fischer Mangold Group (800) 227-2092, or write P.O. Box 788, Pleasanton, CA 94566.

CERTIFIED OR BOARD ELIGIBLE anesthesiologist to join group of 8 at community hospital on Long Island, New York. Early full partnership. Reply Dept. 325, c/o NYSJM.

PHYSICIAN DURING JULY AND AUGUST 1984 for children's camp located at Beach Lake, Pa., accommodates 350 campers, age 6-16; complete modern Health Center; 2 R.N.'s in attendance; will accept one M.D. for each month; no childern accepted who are of camp age. Camp opens June 30 and closes August 24. Private room and facilities. Write (and include your phone number) to Trail's End Camp, c/o Beach Lake, Inc., 215 Adams Street, Brooklyn, N.Y. 11201.

RETIRED PHYSICIAN to work one or one-and-a-half days per week in doctor's weight-control office. Please call Tuesday, Thursday or Friday (212) 358-3310.

INTERNIST WANTED to join a solo practitioner located in Eastern Long Island. Reply Dept. 327, c/o NYSJM.

PHYSICIANS WANTED—CONT'D

GROWING FAMILY PLANNING agency seeks gynecologist (BC/BQ)—Arizona License to supervise abortion clinic services and perform first trimester procedures. Other responsibilities will include assisting medical director in management of contraceptive services provided at 9 sites. 30 hours per week with opportunity for full-time within one year. Salary plus benefits, negotiable. Medical liability insurance provided. EEO/AA Employer. Send CV to: Medical Department, Planned Parenthood of Central and Northern Arizona, 1301 Sth. 7th Avenue, Phoenix, AZ. 85007.

PRACTICES WANTED

INTERNIST, 32, ABIM, with infectious disease subspecialty desires to purchase internal medicine practice in Nassau or Suffolk County. Reply in confidence Dept. 318, c/o NYSJM.

PULMONARY INTERNIST, 33, ABIM completing fellowship July 1984 seeks solo, group, associate, or corporate practice in New York City area. Experienced in bronchoscopy, needle biopsy, pleural biopsy, thoracentesis, ICU, hemodynamics, PFT, etc. Additional experience includes faculty appointment with major teaching university, private practice and administrative responsibilities. Will do internal medicine. Reply Dept. 323, c/o NYSJM.

UROLOGIST Board eligible university trained in adult and pediatric urology. Seeks solo, partnership, group practice in N.Y., N.J. area. Extensive surgical experience in U.S. and overseas. Publications and research experience. Reply to Dept. #319, c/o NYSJM.

OPHTHALMOLOGIST, BOARD CERTIFED, F.A.C.S, F.I.C.S.: wishes to purchase practice in Manhattan. Strictly confidential. Reply to Dept. 294, c/o NYSJM.

OPHTHALMOLOGIST, BOARD Certified F.A.C.S, F.I.C.S., desires to purchase ophthalmology practice in Manhattan. Strictly confidential. Reply to Dept. 306, c/o NYSJM.

INTERNAL MEDICINE. Boston and NYC university hospital trained internist seeking small group practice 1–1½ hours from NYC in NY, CT, NJ. Boston U MD Cum Laude, 1981. ABIM eligible and available July 1984. David L. Oshin, M.D., 30 W 61st St., Apt. 6D, NYC 10023.

OPHTHALMOLOGIST, BOARD CERTIFIED desires to purchase practice in New York City or suburban area. Confidence maintained. Please contact Dept. 168, c/o NYSJM.

OPHTHALMOLOGIST—Board eligible July 1984; board certified pediatrics (1982), age 29, desires partnership or group. Available July 1984. Write Dept. 321, c/o NYSJM.

POSITIONS WANTED

PHYSICIAN ASSISTANTdesires position with orthopedic or general surgeon. 5½ years experience as orthopedic P.A. and in emergency medicine. Will relocate. Please contact S. DiMartino, 70-19 261st St., Glen Oaks, N.Y. 11004. Evenings tel: (516) 488-3199.

MEETINGS AND LECTURES

FEBRUARY 1984

Numerals refer to days of the month

AROUND THE STATE

MANHATTAN

1. **Disabled People and Their Families.** Info: Wanda Brodzka, MD, NY Society of Physical Medicine and Rehabilitation, 136 St and Lenox Ave, New York, NY 10037. Tel: (212) 491-8357.

2. **Emotional Problems in Cancer.** 1½ Cat. 1 credits. Info: Clifford L. Spingarn, MD, Chairman, Committee on CME, Doctors Hospital, 170 East End Ave, New York, NY 10028. Tel: (212) 870-9000.

6–7. **Access to Capital: The Health Market in Flux.** Info: McGraw Hill/ Newsletter Publishing Center Conferences, 1221 Sixth Ave, New York, NY 10020. Tel: (212) 997-4931 or 512-4931.

6–7. New York Downstate I and II Regional Meeting American College of Physicians. Info: Arthur C. Fox, MD, 500 First Ave, New York, NY 10016. Tel: (212) 340-6405.

15. **Clinical Pathology.** 2 Cat. 1 credits. Info: Victor Tchertkoff, MD, Coordinator, Metropolitan Hospital Center, 1901 First Ave, New York, NY 10029. Tel: (212) 360-6253.

15. **Update Your Medicine.** Info: Lila A. Wallis, MD, Association of Practicing Physicians of the New York Hospital, 1300 York Ave, Room D-115, New York, NY 10021. Tel: (212) 737-4444 or Dena Toussaint (212) 472-6119.

16–18. **Surgical Course in Lens Implantation.** Info: Ruth Green, Administrator, Ophthalmological Foundation of America, 345 E. 46 St, New York, NY 10017. (212) 986-4848.

21. **Hypnosis and Hypnotic Techniques: Implications for Liaison Psychiatry.** Info: Mrs. V. Matthes, Administrative Secy, Society for Liaison Psychiatry, 542 Baldwin Ave, Baldwin, NY 11510. Tel: (516) 379-1787.

BRONX

24–25. **Advanced Trauma Life Support Course.** Info: William M. Stahl, Jr, MD, Chairman, New York/Brooklyn Com-

(*continued on page 12A*)

Doctor . .

Do you, or a physician you know, have a problem with alcoholism, drug abuse, emotional illness or other difficulties which interfere with the ability to practice medicine?

If so, please contact the Medical Society of the State of New York's Physicians' Committee, whose function is to assist impaired physicians, at the following confidential number: 516-488-7777.

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Pfizer Laboratories 18A,19A

Roche Laboratories .... 3rd & 4th Covers

Upjohn Company 1A

U. S. Navy 8A

Wyeth Laboratories 15A,16A

(*continued from page 11A*)

mittee on Trauma, Lincoln Medical Mental Health Center, 234 E. 149 St, Bronx, NY 10451. Tel: (212) 579-5000.

BROOKLYN

1. **Nutrition and Cancer Prevention.** *8.* **Postmastectomy Lymphedema.** *15.* **Malignant Lymphomas.** *22.* **Primary Breast Cancer: Controversies in Treatment.** *29.* **Thalassemia Syndrome.** 1 Cat. 1 credit per lecture. Info: Harvey Dosik, MD, Interfaith Medical Center, 555 Prospect Place, Brooklyn, NY 11238. Tel: (212) 240-1211, or 1212.

14. **Anesthesia for Patients with Congenital Heart Disease.** *15.* **Anesthetic Considerations in Patients Undergoing Vascular Surgery.** 1 Cat. 1 credit per lecture. Info: Abraham I. Raskob, MD, Chairman, CME Committee, SUNY Downstate Medical Center, Dept of Anesthesiology, 450 Clarkson Ave, Brooklyn, NY 11203. Tel: (212) 270-1233.

19. **Clinical Preventive Medicine.** Info: Doris Graber, Kings County Medical Society, 1313 Bedford Ave, Brooklyn, NY 11216. Tel: (212) 467-9000.

QUEENS

2. **Immunization Update.** *9.* **Human Milk in Infant Nutrition.** *16.* **Viral Hepatitis.** *23.* **Hypertension.** 1 Cat. 1 credit per lecture. Info: Clo Vezza, CME, Booth Memorial Medical Center 56-45 Main Street, Flushing, NY 11355. Tel: (212) 670-1419.

NASSAU

3. **Short-Term Dynamic Psychotherapy.** 7 Cat. 1 credits. *22.-June 13.* **Pediatric Board Review.** 32 Cat. 1 credits. Info: Ann J. Boehme, CME, Long Island Jewish-Hillside Medical Center, New Hyde Park, NY 11042. Tel: (212) 470-2114.

16. **Radiology of Iatrogenic Complications of Pediatric Surgery.** Info: M. Pochaczevsky, MD, Dept of Radiology, Long Island Jewish-Hillside Medical Center, New Hyde Park, NY 11042. Tel: (212) 240-2441.

3. **An Interactional Approach to the Patients with Developmental Arrest.** *10.* **Hypnosis: Clinical Perspectives.** *17.* **Concepts of Piaget.** *24.* **Incest: Victims and Offenders.** Info: Clement Boccalini, MD, Nassau County Medical Center, 2201 Hempstead Turnpike, East Meadow, NY 11554. (516) 542-0123.

21. **Gynecologic Urology.** 4 Cat. 1 credits. Info: Mary Leong, MD, Assist Dir of Gynecology, Nassau County Medical Center, 2201 Hempstead Turnpike, E. Meadow, NY 11554. (516) 542-2256.

SUFFOLK

7. **The Sick Newborn in the Community Hospital. 14. Pediatric Gastroenterology.** Info: Arthur Schwager, MD, Huntington Hospital, 270 Park Ave, Huntington, NY 11743. Tel: (516) 427-0530.

ALBANY

23–26. **Critical Care Symposium.** Albany. Info: Elizabeth Damm, Conference Coordinator, Ellis Hospital, 1101 Nott St, Schenectady, NY 12308. Tel: (518) 382-4135.

ERIE

11. **Advances in Cancer Chemotherapy.** Info: Gayle Bersani, RN, Roswell Park Memorial Institute, 666 Elm St, Buffalo, NY 14263. (716) 845-4406.

ROCKLAND

7. **Beta Blockade in the 1980s.** *14.* **Electrophysiologic Testing in the Evaluation of Syncope.** *21.* **Evaluation of the Post MI Patient.** *28.* **The Expanding Role of Exercise Radionuclide Ventriculography in Patient Management.** Info: Clinical Dept Directors' Office, Nyack Hospital, North Midland Ave, Nyack, NY 10960. Tel: (914) 358-6200, x-2509.

AROUND THE NATION

CALIFORNIA

13–17. **Topics in Internal Medicine.** 36 Cat. 1 credits. Info: Medicine, Education and Research Foundation, Department of Medicine, U of Cal, San Diego, PO Box 81344, San Diego, CA 92138. Tel: (619) 297-3233.

16–17. **Institutional Ethics Committees and Healthcare Decisionmaking.** Los Angeles. Info: American Society of Law & Medicine, 765 Commonwealth Ave, 16th floor, Boston, MA 02215. Tel: (617) 262-4990.

19–22. **Recombinant DNA Research.** San Diego. Info: DNA Congress, c/o Scherago Associates, Inc., 1515 Broadway, New York, NY 10036. Tel: (212) 730-1050.

18–22. **Delicate Balance between Humanity and Technology.** 32 Cat. 1 credits. Info: Ms Orienne Strode, Director, Human Dimensions in Medical Education, 1125 Torrey Pines Road, La Jolla, CA 92037. (619) 459-3861.

24–25. **Intra-Arterial and Intracavitary Chemotherapy.** San Diego. 15 Cat. 1 credits. Info: Catherine M. Petocchi, CME, U of Cal, San Diego School of Medicine, M-017, La Jolla, CA 92093. Tel: (619) 452-3940.

COLORADO

5–11. **Hematology and Oncology Update.** Steamboat. 20 Cat. 1 credits. Info: Program Coordinator, Office of Continuing Education, Upstate Medical Center, State University of New York, 750 E Adams St, Syracuse, NY 13210. Tel: (315) 473-4304.

13–17. **Clinical Approach to Disturbances of Fluid, Electrolyte and Acid-Base Balance.** Vail. *20–24.* **Problems in Gastroenterology: A Clinial & Pathological Approach.** Keystone. *27–2 Mar.* **Pregnancy and the Internist.** Breckenridge. Info: Registrar, American College of Physicians, 4200 Pine St, Philadelphia, PA 19104. Tel: (215) 243-1200.

25–3 Mar. **Pulmonary and Critical Care Medicine.** Aspen. 22 Cat. 1 credits. Info: Extended Programs in Medical Education. U of Cal, San Francisco, CA 94143. Tel: (415) 666-5808.

FLORIDA

5–10. **Internal Medicine.** Bal Harbour. 37½ Cat. 1 credits. Info: Jose S Bocles, MD, Department of Medicine (R760), U. of Miami School of Medicine, PO Box 016760, Miami, FL 33101. (305) 547-6063.

9–11. **Perspectives in Allergy and Rheumatology.** Sarasota. Info: Registrar, American College of Physicians, 4200 Pine Street, Philadelphia, PA 19104. Tel: (215) 243-1200.

9–12. **Advances in Pediatric Gastroenterology and Nutrition.** Fort Lauderdale. 20 Cat. 1 credits. Info: Rayna Dutton, CME, Children's Hospital, 219 Bryant St, Buffalo, NY 14222. Tel: (collect) (716) 878-7630 or 7640.

17–18. **Oncology Update.** 12 Cat. 1 credits. Miami. Info: Ms Thelma MacGregor, Medical Education, Cedar Medical Center, 1400 NW 12th Ave, Miami, FL 33136. Tel: (305) 325-5511.

23–26. **Pediatric Dermatology Seminar.** Miami Beach. Info: Guinter Kahn, MD, 16800 NW 2nd Ave, #401, N Miami Beach, FL 33169. Tel: (305) 652-8600.

(*continued on page 16A*)

We Invite You to Join the
American Physicians Fellowship
which helps to make
ISRAEL
a world Medical Center

- grants FELLOWSHIPS to selected Israeli physicians for postgraduate study in the United States or Canada
- built and maintains Jerusalem Academy of Medicine and Israel Institute of the History of Medicine in Jerusalem
- Conducts annual superior medical seminars in the four medical centers of Israel. Also provides annual seminar in Florida in general medicine during the last week of February
- Supplies SEED money for original medical research in Israel
- Coordinates the medical and paramedical emergency volunteers from the United States and Canada to aid Israel during a time of crisis, etc.

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Application for Membership
American Physicians Fellowship, Inc.

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Birthplace__________Date of Birth__________

Medical School__________Year__________

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Specialty__________

Proposed by__________

Signature__________

Annual dues of $35.00 is herewith enclosed.
(tax deductible)

He Thought That Drinking Wouldn't Make Any Difference, Even Though He Was on a New Medication. But It Did.

Now he knows that alcohol and some medicines don't mix. In fact, more than half the 100 most prescribed drugs have at least one ingredient that can cause trouble if taken while drinking alcohol. The result of mixing these drugs (alcohol is a drug) may be no more than simple temporary illness, but some combinations can be dangerous, even deadly.

So, don't make a test tube out of your body. Be sure to tell your doctor or druggist about any medications you are taking and be sure to ask about the consequences of mixing a newly prescribed drug with alcohol.

Also, make it a habit to check the label carefully when you get a drug, whether it's a prescription or over-the-counter medication.

And when you get any prescription, be sure you know—

- **The name** of the drug
- **Its purpose**—what conditions does it treat?
- **How and when** to take the drug—and when to stop taking it
- What **food, drinks and other drugs to avoid** while taking it
- What **side effects** may result—are they serious, short-term, long-term, etc.?

If you have any questions about your prescription, *ask your doctor or pharmacist.*

A message from the Food and Drug Administration. For more material about being an informed patient, write to: FDA, HFE-88, Rockville, Md. 20857.

EQUIPMENT

COMBINED OTOLARYNGOLOGIST AND Ophthalmologist, recently retired has office equipment, instruments and textbooks for sale. Write or call Jerome Lehner, M.D., 141 Hooker Avenue, Poughkeepsie, New York 12601.

PRACTICES AVAILABLE

URGENTLY NEEDED—FAMILY PHYSICIAN in rural Central New York community. 40 year old practice for sale due to retirement. Excellent location, large attractive home-office combination. Hospitals nearby in Oswego, Fulton, Syracuse, N.Y. Call evenings (315) 963-7512 or (315) 963-8565.

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MISCELLANEOUS

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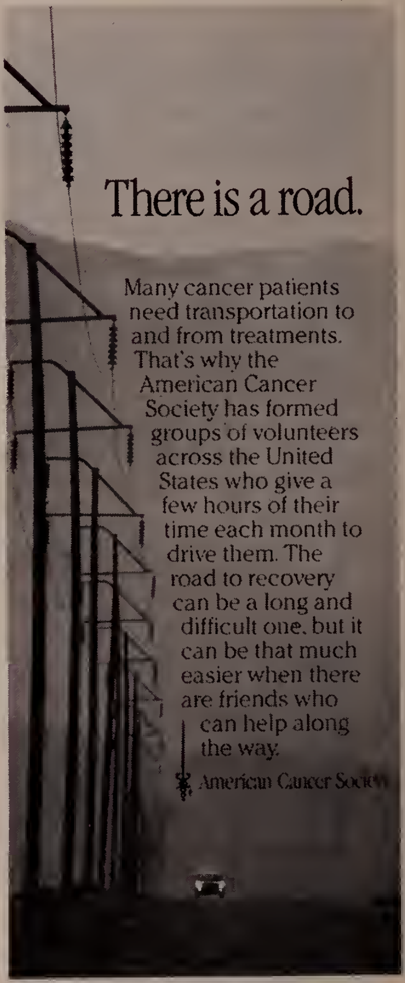

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American Cancer Society

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Agent of change

Ativan®

for (lorazepam) Ⓒ **Anxiety**

See important information on following page.

*All benzodiazepines produce additive sedative effects when given with alcohol or other CNS depressants.

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NEW TABLET DESIGN 0.5, 1.0 and 2.0 mg

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy shoold be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

Ativan® Ⓒ‑IV
for (lorazepam)
Anxiety

DOSAGE: Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.

HOW SUPPLIED: 0.5, 1.0 and 2.0mg tablets.

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(continued from page 12A)

MARYLAND

2–4. **Two-Dimensional and Doppler Echocardiographic Diagnosis of Congenital Heart Disease in Children.** 17 Cat. 1 credits. *13–15.* **Rehabilitation of the Coronary Patient.** 19 Cat. 1 credits. *29–2 Mar.* **Cardiac Disease and Its Therapy: The Role of Development and Aging.** 17 Cat. 1 credits. Bethesda. Info: Ronald J. Sanchez, Dir of Comm, 9111 Old Georgetown Road, Bethesda, MD 20814. Tel: (301) 897-5400.

24–25. **Tuberculosis Symposium.** 11 Cat. 1 credits. Baltimore. Info: Velma B. Rector, American Lung Association of MD, 11 E Mt Royal Ave, Baltimore, MD 21202. (301) 685-6484.

TEXAS

2–5. **Southwest Allergy Forum.** Houston. Info: Carol Soroka, Office of Continuing Education, Baylor College of Medicine, Texas Medical Center, Houston, TX 77030. Tel: (713) 799-6020.

22–26. **American Group Psychotherapy Association Annual Meeting.** Dallas. Info: AGPA, 1995 Broadway, 14th Floor, New York, NY 10023. Tel: (212) 787-2618.

VERMONT

19–23. **Medical Seminar.** 18 Cat. 1 credits. Sugarbush. Info: Office of Continuing Education, Tufts U School of Medicine, Box 36, 136 Harrison Ave, Boston, MA 02111. (617) 956-6579.

26–2 Mar. **Tutorial in Cardiology.** 18 Cat. 1 credits. Sugarbush. Info: Division of Cardiology, U of Vermont, School of Medicine, Burlington, VT 05405. Tel: (802) 656-2558.

AROUND THE WORLD

JAMAICA

18–25. **International Oculoplastic Society Congress and International Facial Surgery Seminar.** Info: Ms J. Weschner, c/o P. Guibor, MD, 630 Park Ave, New York, NY 10021. Tel: (212) 734-1010.

MEXICO

26–3 Mar. **Imaging of the CNS and Spine: CT, NMR, Digital, Interventional.** 25 Cat. 1 credits. Info: Betty Frost, Program Coordinator, Office of Continuing Education, SUNY, Upstate Medical Center, 766 Irving Ave, Syracuse, NY 13210. Tel: (315) 473-4606.

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MISCELLANEOUS—CONT'D

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References:

1. Stone PH, Turi ZG, Muller JE: Efficacy of nifedipine therapy for refractory angina pectoris. *Am Heart J* 104:672-681, September 1982.
2. Antman E, Muller J, Goldberg S, et al: Nifedipine therapy for coronary-artery spasm: Experience in 127 patients. *N Engl J Med* 302:1269-1273, June 5, 1980.

BRIEF SUMMARY

PROCARDIA® (nifedipine) **CAPSULES** For Oral Use

INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in those patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See Warnings.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving PROCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PROCARDIA and a beta blocker, but the possibility that it may occur with PROCARDIA alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In PROCARDIA treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for PROCARDIA to be washed out of the body prior to surgery.

Increased Angina: Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Beta Blocker Withdrawal: Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients, usually receiving a beta blocker, have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See Warnings.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Drug interactions: Beta-adrenergic blocking agents: (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing PROCARDIA to avoid possible over- or under-digitalization.

Carcinogenesis, mutagenesis, impairment of fertility: When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose.

Pregnancy: Category C. Please see full prescribing information with reference to teratogenicity in rats, embryotoxicity in rats, mice and rabbits, and abnormalities in monkeys.

ADVERSE REACTIONS: The most common adverse events include dizziness or light-headedness, peripheral edema, nausea, weakness, headache and flushing each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Additionally, the following have been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, diarrhea, constipation, inflammation, joint stiffness, shakiness, sleep disturbances, blurred vision, difficulties in balance, dermatitis, pruritus, urticaria, fever, sweating, chills, and sexual difficulties. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

Laboratory Tests: Rare, mild to moderate, transient elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted, and a single incident of significantly elevated transaminases and alkaline phosphatase was seen in a patient with a history of gall bladder disease after about eleven months of nifedipine therapy. The relationship to PROCARDIA therapy is uncertain. These laboratory abnormalities have rarely been associated with clinical symptoms. Cholestasis, possibly due to PROCARDIA therapy, has been reported twice in the extensive world literature.

HOW SUPPLIED: Each orange, soft gelatin PROCARDIA CAPSULE contains 10 mg of nifedipine. PROCARDIA CAPSULES are supplied in bottles of 100 (NDC 0069-2600-66), 300 (NDC 0069-2600-72), and unit dose (10x10) (NDC 0069-2600-41). The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

More detailed professional information available on request

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"I can do things that I couldn't do for 3 yrs. including joining the human race again."

*Quotes from an unsolicited letter received by Pfizer from an angina patient.
While this patient's experience is representative of many unsolicited comments received, not all patients will respond to Procardia nor will they all respond to the same degree.*

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"My daily routine consisted of sitting in my chair trying to stay alive."

"My doctor switched me to PROCARDIA[*] *as soon as it became available. The change in my condition is remarkable."*

"I shop, cook and can plant flowers again."

"I have been able to do volunteer work...and feel needed and useful once again."

PROCARDIA can mean the return to a more normal life for your patients—having fewer anginal attacks,[1] taking fewer nitroglycerin tablets,[2] doing more, and being more productive once again.

Side effects are usually mild (most frequently reported are dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%).

for the varied faces of angina

PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

*Procardia is indicated for the management of:
1) Confirmed vasospastic angina.
2) Angina where the clinical presentation suggests a possible vasospastic component.
3) Chronic stable angina without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or nitrates or who cannot tolerate these agents. In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks' duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

Please see PROCARDIA *brief summary on adjoining page.*

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Apr.-Sept. 1984
4-7 p.m.
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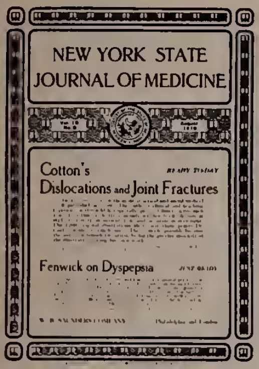
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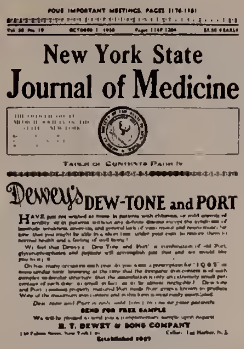
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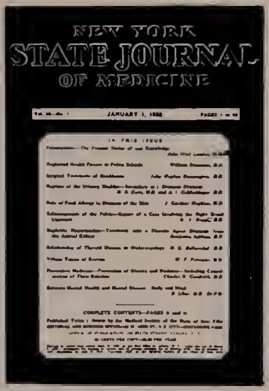
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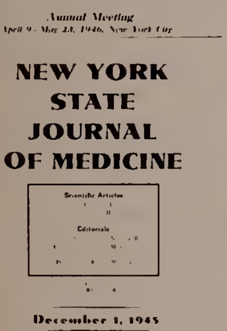
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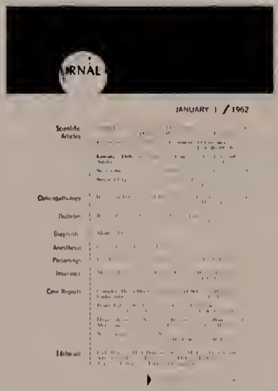
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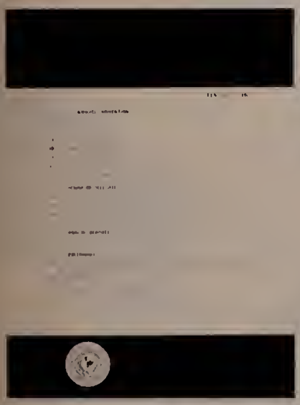

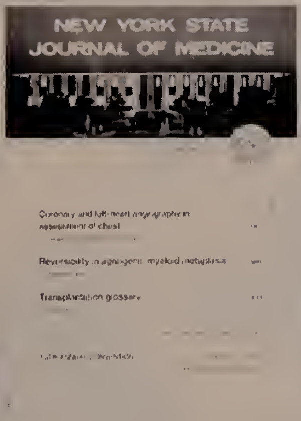
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	Cancer Update, Versailles Terrace
	Pediatrics/School Health, Royal Ballroom B
	Meet the Professor, Consulate Suite Regency Foyer
Afternoon	Pediatrics/School Health, Royal Ballroom B (all day)
	Neurosurgery, Versailles Terrace
	Medical Legal & Workers' Compensation/Occupational Medicine, Royal Ballroom A
	Neurology, Regency Ballroom
	Meet the Professor, Consulate Suite Regency Foyer

SATURDAY, JUNE 30

Morning	Chest Diseases, Regency Ballroom
	Internal Medicine, Georgian Ballroom A (all day)
	Ophthalmology, Royal Ballroom A (all day)
	General Session "Violence", Georgian Ballroom B (all day)
	Obstetrics/Gynecology, Versailles Terrace
	Hand Surgery, Royal Ballroom B (all day)
Afternoon	Internal Medicine, Georgian Ballroom A
	Ophthalmology, Royal Ballroom A
	General Session "Violence", Georgian Ballroom B
	Dermatology/Otolaryngology, Versailles Terrace
	Pathology/Gastroenterology, Regency Ballroom
	Hand Surgery, Royal Ballroom B

SUNDAY, JULY 1

Morning	Allergy & Immunology, Georgian Ballroom A
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	Orthopedic Surgery/General Surgery/Plastic Surgery/Physical Medicine & Rehabilitation/Radiology/Anesthesiology, Georgian Ballroom B (all day)
	Urology/Emergency Medicine, Royal Ballroom A
	Women's Medical Society of New York State, Versailles Terrace
Afternoon	Family Practice/Preventive Medicine/Psychiatry, Royal Ballroom B
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References: **1.** Kales A *et al: J Clin Pharmacol 17:*207-213, Apr 1977 and data on file, Hoffmann-La Roche Inc., Nutley, NJ. **2.** Kales A: Data on file, Hoffmann-La Roche Inc., Nutley, NJ. **3.** Zimmerman AM: *Curr Ther Res 13:*18-22, Jan 1971. **4.** Kales A *et al: JAMA 241:*1692-1695, Apr 20, 1979. **5.** Kales A, Scharf MB, Kales JD: *Science 201:*1039-1041, Sep 15, 1978. **6.** Kales A *et al: Clin Pharmacol Ther 19:*576-583, May 1976. **7.** Kales A, Kales JD: *Pharmacol Physicians 4:*1-6, Sep 1970. **8.** Frost JD Jr, DeLucchi MR: *J Am Geriatr Soc 27:*541-546, Dec 1979. **9.** Dement WC *et al: Behav Med 5:*25-31, Oct 1978. **10.** Vogel GW: Data on file, Hoffmann-La Roche Inc., Nutley, NJ. **11.** Karacan I, Williams RL, Smith JR: The sleep laboratory in the investigation of sleep and sleep disturbances. Scientific exhibit at the 124th annual meeting of the American Psychiatric Association, Washington, DC, May 3-7, 1971. **12.** Pollak CP, McGregor PA, Weitzman ED: The effects of flurazepam on daytime sleep after acute sleep-wake cycle reversal. Presented at the 15th annual meeting of the Association for Psychophysiological Study of Sleep, Edinburgh, Scotland, June 30-July 4, 1975. **13.** Data on file, Hoffmann-La Roche Inc., Nutley, NJ.

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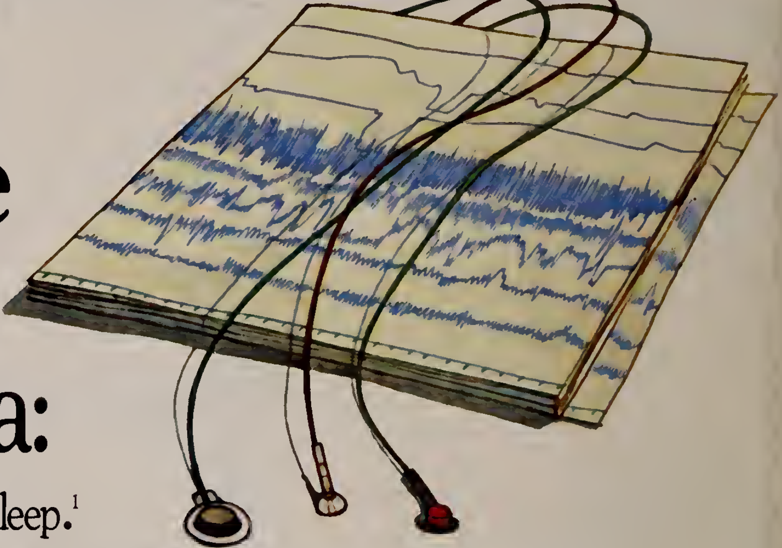

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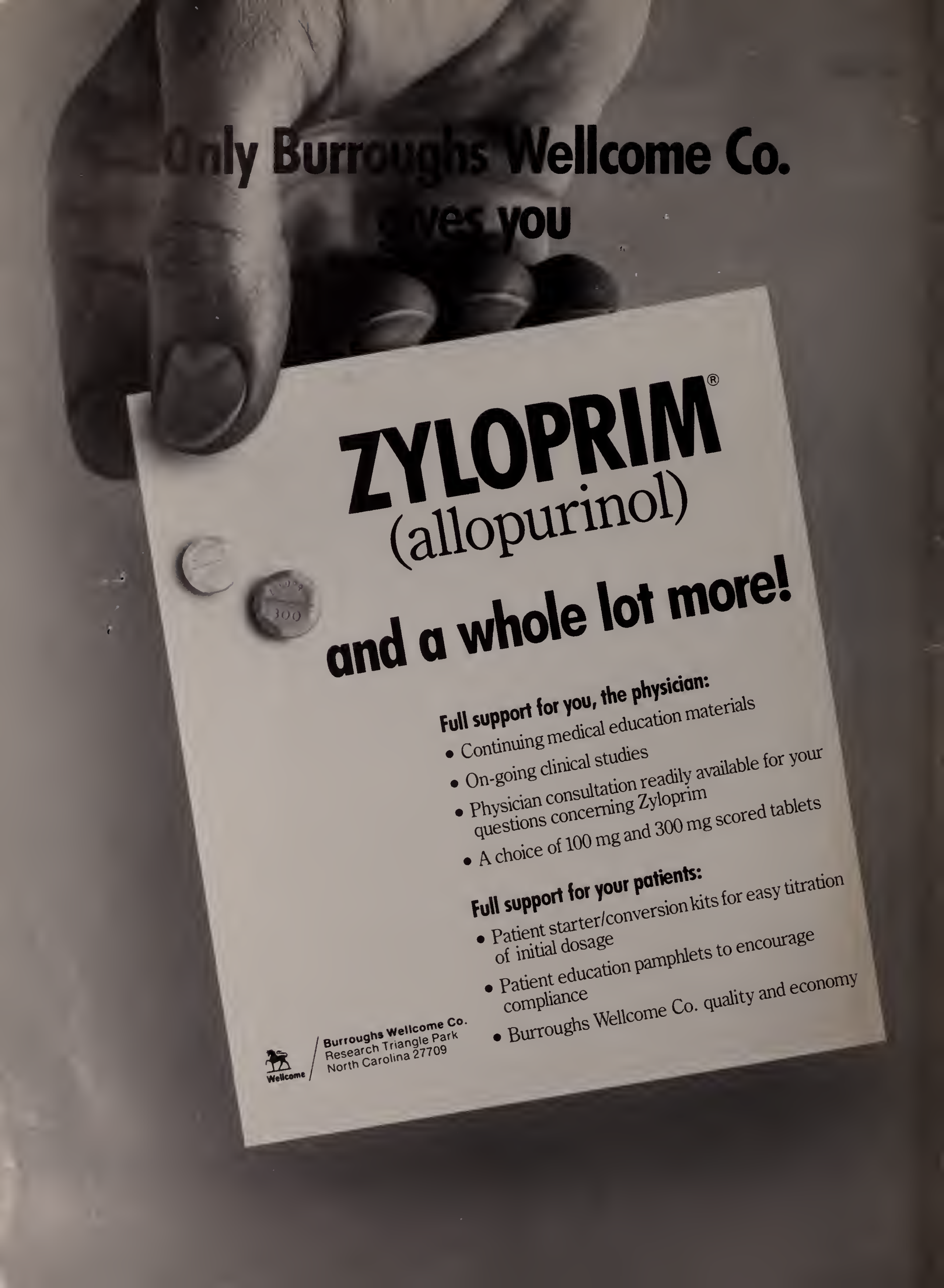

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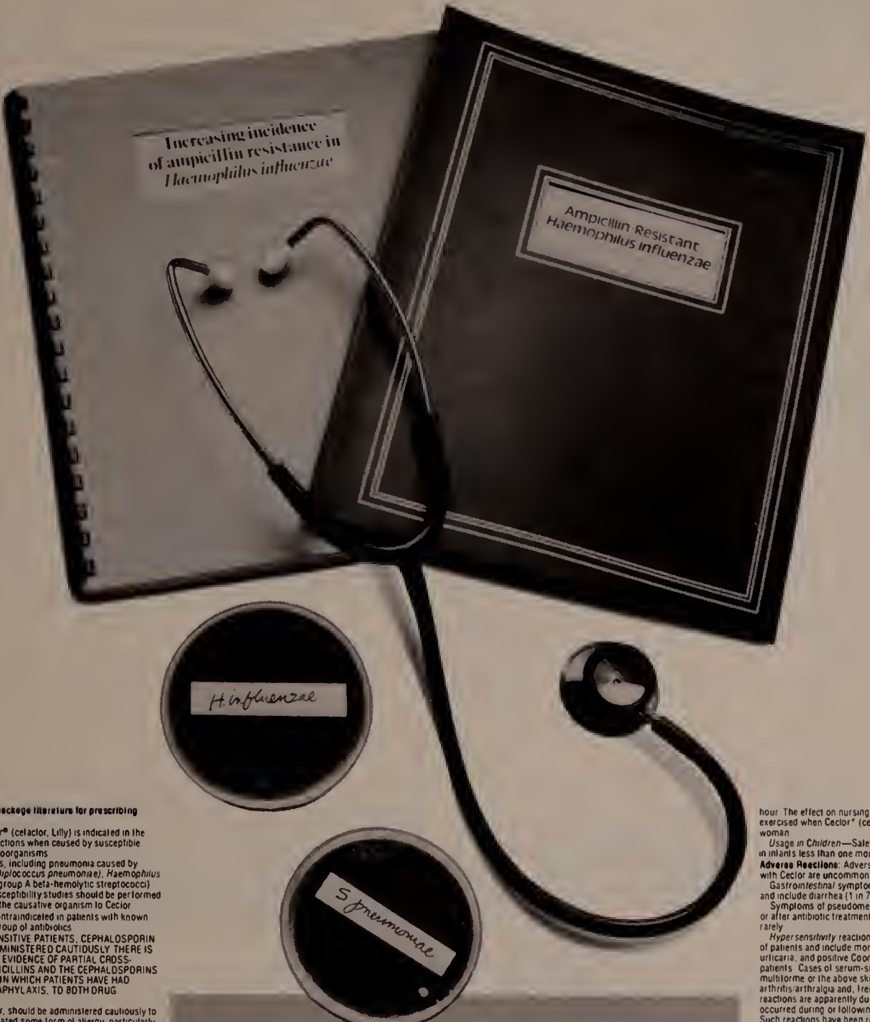
An added complication... in the treatment of bacterial bronchitis*


Increasing incidence of ampicillin resistance in Haemophilus influenzae
Ampicillin Resistant Haemophilus influenzae
H. influenzae
S. pneumoniae

Some ampicillin-resistant strains of Haemophilus influenzae—a recognized complication of bacterial bronchitis*—are sensitive to treatment with Ceclor.[1-6]

In clinical trials, patients with bacterial bronchitis due to susceptible strains of Streptococcus pneumoniae, H. influenzae, S. pyogenes (group A beta-hemolytic streptococci), or multiple organisms achieved a satisfactory clinical response with Ceclor.[7]

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Pulvules®, 250 and 500 mg

Brief Summary. Consult the package literature for prescribing information.

Indications and Usage: Ceclor® (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae (Diplococcus pneumoniae)*, *Haemophilus influenzae*, and *S pyogenes* (group A beta-hemolytic streptococci)

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins), therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics Such colitis may range in severity from mild to life-threatening

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation When the colitis does not improve after the drug has been discontinued, or when it is severe oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile* Other causes of colitis should be ruled out

Precautions: *General Precautions*—If an allergic reaction to Ceclor occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e g , pressor amines, antihistamines, or corticosteroids

Prolonged use of Ceclor may result in the overgrowth of nonsusceptible organisms Careful observation of the patient is essential If superinfection occurs during therapy, appropriate measures should be taken

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs test may be due to the drug

Ceclor should be administered with caution in the presence of markedly impaired renal function Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly)

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis

Usage in Pregnancy—Pregnancy Category B—Reproduction studies have been performed in mice and rats at doses up to 12 times the human dose and in ferrets given three times the maximum human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Ceclor There are, however, no adequate and well-controlled studies in pregnant women Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Nursing Mothers—Small amounts of Ceclor have been detected in mother's milk following administration of single 500-mg doses Average levels were 0 18, 0 20, 0 21, and 0 16 mcg/ml at two, three four, and five hours respectively Trace amounts were detected at one hour The effect on nursing infants is not known Caution should be exercised when Ceclor® (cefaclor, Lilly) is administered to a nursing woman

Usage in Children—Safety and effectiveness of this product for use in infants less than one month of age have not been established

Adverse Reactions: Adverse effects considered related to therapy with Ceclor are uncommon and are listed below

Gastrointestinal symptoms occur in about 2 5 percent of patients and include diarrhea (1 in 70)

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment Nausea and vomiting have been reported rarely

Hypersensitivity reactions have been reported in about 1 5 percent of patients and include morbilliform eruptions (1 in 100) Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever) have been reported These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Ceclor Such reactions have been reported more frequently in children than in adults Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy No serious sequelae have been reported Antihistamines and corticosteroids appear to enhance resolution of the syndrome

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients)

Causal Relationship Uncertain—Transitory abnormalities in clinical laboratory test results have been reported Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician

Hepatic—Slight elevations of SGOT, SGPT, or alkaline phosphatase values (1 in 40)

Hematopoietic—Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40)

Renal—Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200)

[061782R]

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*Many authorities attribute acute infectious exacerbation of chronic bronchitis to either *S pneumoniae* or *H influenzae* [8]

Note Ceclor is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever See prescribing information

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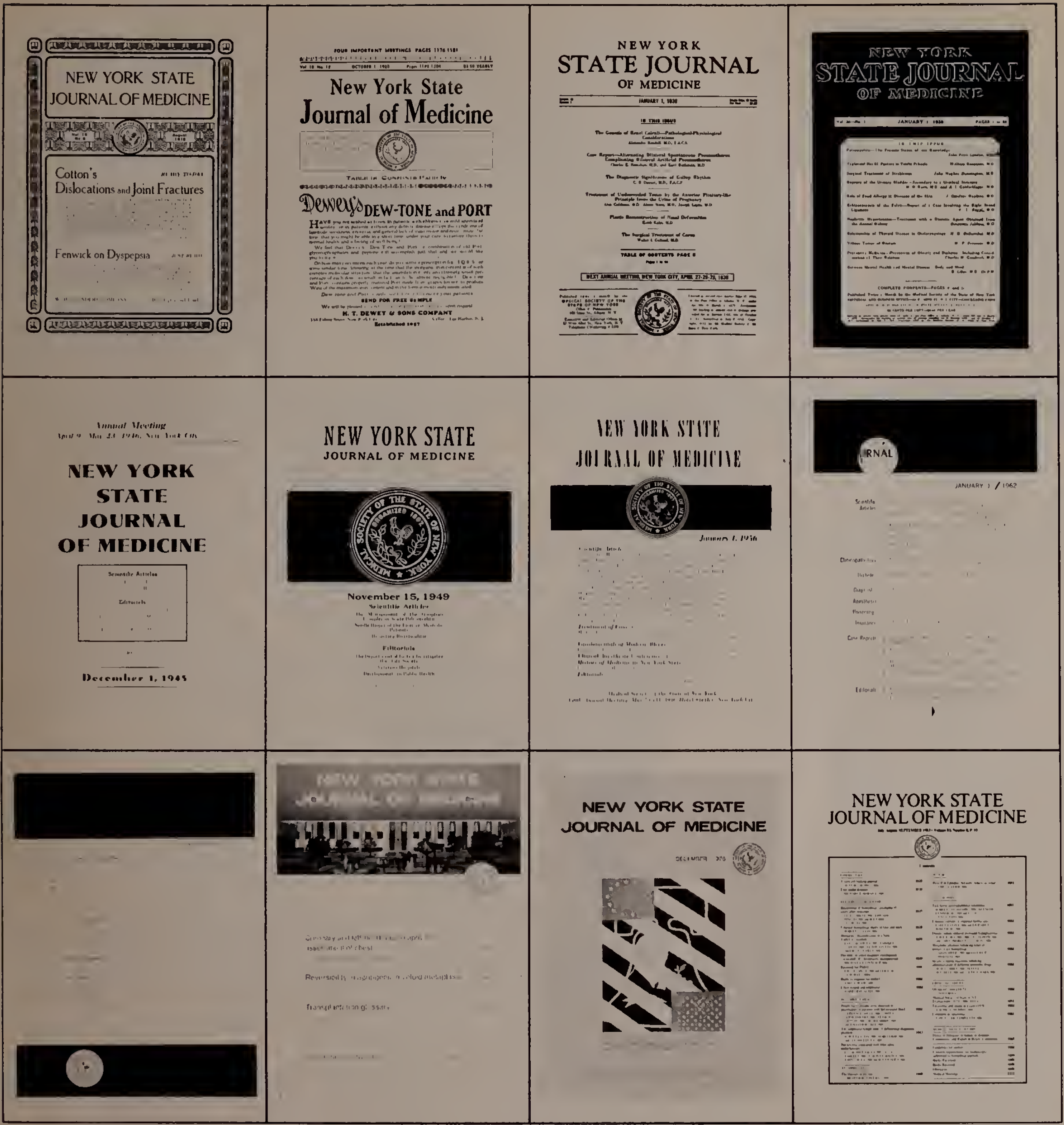
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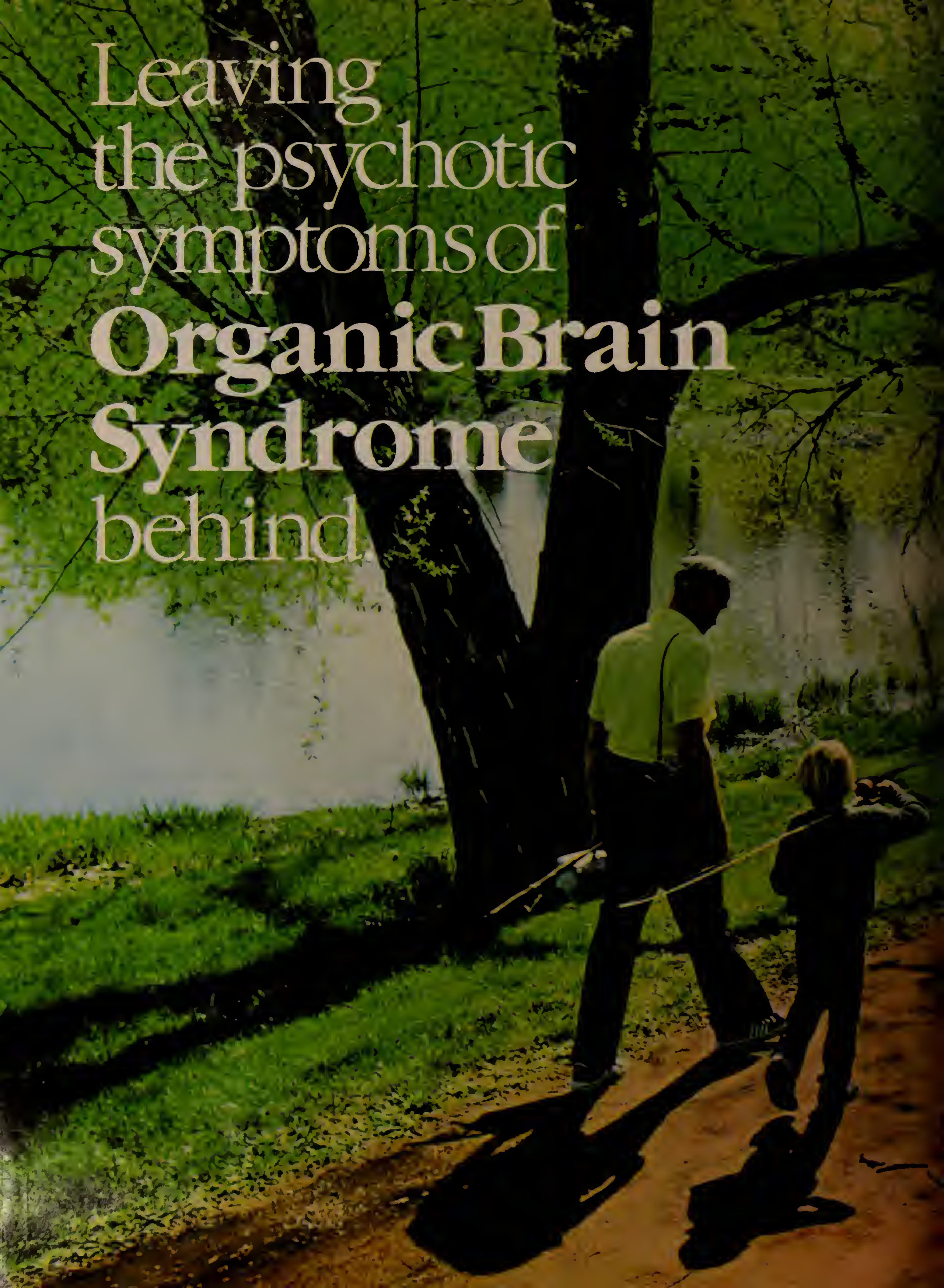
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Well tolerated

Navane is generally well tolerated by elderly patients. Excessive sedation or drowsiness has been reported, but is uncommon.[1] Anticholinergic effects[3] and hypotension[4,5] are reported, but rarely. Should they occur, extrapyramidal symptoms can usually be readily controlled.

Navane®

(thiothixene) (thiothixene HCl)

Capsules 1 mg, 2 mg, 5 mg, 10 mg, 20 mg
Concentrate 5 mg/ml Intramuscular 2 mg/ml, 5 mg/ml

See following page for a brief summary of prescribing information

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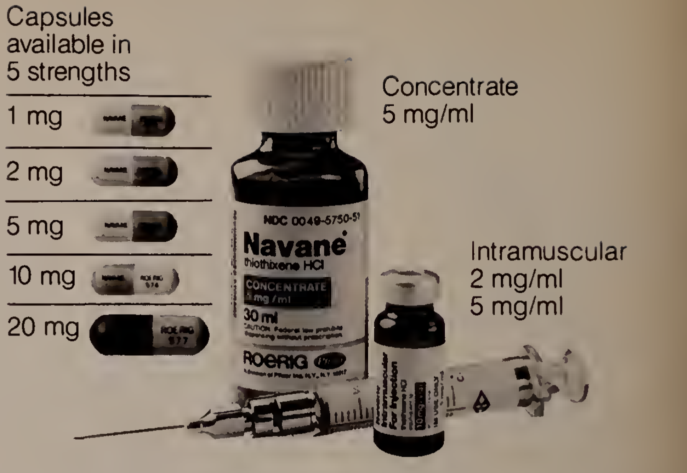

BRIEF SUMMARY OF PRESCRIBING INFORMATION
Navane® (thiothixene) Capsules: 1 mg, 2 mg, 5 mg, 10 mg, 20 mg
(thiothixene hydrochloride) Concentrate: 5 mg/ml, intramuscular: 2 mg/ml, 5 mg/ml

Contraindications: Navane (thiothixene) is contraindicated in patients with circulatory collapse, comatose states, central nervous system depression due to any cause, and blood dyscrasias Navane is contraindicated in individuals who have shown hypersensitivity to the drug It is not known whether there is a cross-sensitivity between the thioxanthenes and the phenothiazine derivatives, but the possibility should be considered

Warnings: *Usage in Pregnancy* – Safe use of Navane during pregnancy has not been established Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus Animal reproduction studies and clinical experience to date have not demonstrated any teratogenic effects

In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, *no* teratogenic effects were seen. (See Precautions.)

Usage in Children – The use of Navane in children under 12 years of age is not recommended because safety and efficacy in the pediatric age group have not been established

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy Therefore, the patient should be cautioned accordingly

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol

Precautions: An antiemetic effect was observed in animal studies with Navane, since this effect may also occur in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumor.

In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold. Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered concurrently

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with other CNS depressants other than anticonvulsant drugs.

Though exhibiting rather weak anticholinergic properties, Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving atropine or related drugs

Use with caution in patients with cardiovascular disease.

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine lenticular pigmentation has been noted in a small number of patients treated with Navane for prolonged periods) Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenic purpura), and liver damage (jaundice, biliary stasis) have been reported with related drugs.

Undue exposure to sunlight should be avoided Photosensitive reactions have been reported in patients on Navane.

Neuroleptic drugs elevate prolactin levels, the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance' if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis, the available evidence is considered too limited to be conclusive at this time.

Intramuscular Administration – As with all intramuscular preparations, Navane Intramuscular should be injected well within the body of a relatively large muscle The preferred sites are the upper outer quadrant of the buttock (i.e gluteus maximus) and the mid-lateral thigh.

The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-thirds of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.

Adverse Reactions: *Note:* Not all of the following adverse reactions have been reported with Navane (thiothixene) However, since Navane has certain chemical and pharmacologic similarities to the phenothiazines, all of the known side effects and toxicity associated with phenothiazine therapy should be borne in mind when Navane is used

Cardiovascular effects Tachycardia, hypotension, lightheadedness, and syncope In the event hypotension occurs, epinephrine should not be used as a pressor agent since a paradoxical further lowering of blood pressure may result Nonspecific EKG changes have been observed in some patients receiving Navane These changes are usually reversible and frequently disappear on continued Navane therapy The incidence of these changes is lower than that observed with some phenothiazines The clinical significance of these changes is not known.

CNS effects Drowsiness, usually mild, may occur although it usually subsides wtih continuation of Navane therapy The incidence of sedation appears similar to that of the piperazine group of phenothiazines, but less than that of certain aliphatic phenothiazines. Restlessness, agitation and insomnia have been noted with Navane (thiothixene). Seizures and paradoxical exacerbation of psychotic symptoms have occurred with Navane infrequently

Hyperreflexia has been reported in infants delivered from mothers having received structurally related drugs.

In addition, phenothiazine derivatives have been associated with cerebral edema and cerebrospinal fluid abnormalities

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia, and dystonia have been reported Management of these extrapyramidal symptoms depends upon the type and severity Rapid relief of acute symptoms may require the use of an injectable antiparkinson agent More slowly emerging symptoms may be managed by reducing the dosage of Navane and/or administering an oral antiparkinson agent

Persistent Tardive Dyskinesia: As with all antipsychotic agents tardive dyskinesia may appear in some patients on long term therapy or may occur after drug therapy has been discontinued. The risk seems to be greater in elderly patients on high-dose therapy, especially females The symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities

There is no known effective treatment for tardive dyskinesia, antiparkinsonism agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear

Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, the syndrome may be masked.

It has been reported that fine vermicular movements of the tongue may be an early sign of the syndrome and if the medication is stopped at that time, the syndrome may not develop.

Hepatic effects: Elevations of serum transaminase and alkaline phosphatase, usually transient, have been infrequently observed in some patients. No clinically confirmed cases of jaundice attributable to Navane (thiothixene) have been reported.

Hematologic effects: As is true with certain other psychotropic drugs, leukopenia and leukocytosis, which are usually transient, can occur occasionally with Navane. Other antipsychotic drugs have been associated with agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopenia

Allergic reactions: Rash, pruritus, urticaria, photosensitivity and rare cases of anaphylaxis have been reported with Navane Undue exposure to sunlight should be avoided Although not experienced with Navane, exfoliative dermatitis and contact dermatitis (in nursing personnel) have been reported with certain phenothiazines

Endocrine disorders: Lactation, moderate breast enlargement and amenorrhea have occurred in a small percentage of females receiving Navane. If persistent, this may necessitate a reduction in dosage or the discontinuation of therapy Phenothiazines have been associated with false positive pregnancy tests, gynecomastia, hypoglycemia, hyperglycemia, and glycosuria

Autonomic effects: Dry mouth, blurred vision, nasal congestion, constipation, increased sweating, increased salivation, and impotence have occurred infrequently with Navane therapy. Phenothiazines have been associated with miosis, mydriasis, and adynamic ileus.

Other adverse reactions: Hyperpyrexia, anorexia, nausea, vomiting, diarrhea, increase in appetite and weight, weakness or fatigue, polydipsia and peripheral edema

Although not reported with Navane, evidence indicates there is a relationship between phenothiazine therapy and the occurrence of a systemic lupus erythematosus-like syndrome.

NOTE: Sudden deaths have occasionally been reported in patients who have received certain phenothiazine derivatives In some cases the cause of death was apparently cardiac arrest or asphyxia due to failure of the cough reflex. In others, the cause could not be determined nor could it be established that death was due to phenothiazine administration

Dosage and Administration: Dosage of Navane should be individually adjusted depending on the chronicity and severity of the condition In general, small doses should be used initially and gradually increased to the optimal effective level, based on patient response.

Some patients have been successfully maintained on once-a-day Navane therapy

Usage in children under 12 years of age is not recommended because safe conditions for its use have not been established

Navane Intramuscular Solution: Navane For Injection – Where more rapid control and treatment of acute behavior is desirable, the intramuscular form of Navane may be indicated It is also of benefit where the very nature of the patient's symptomatology, whether acute or chronic, renders oral administration impractical or even impossible.

For treatment of acute symptomatology or in patients unable or unwilling to take oral medication, the usual dose is 4 mg of Navane Intramuscular administered 2 to 4 times daily Dosage may be increased or decreased depending on response. Most patients are controlled on a total daily dosage of 16 to 20 mg. The maximum recommended dosage is 30 mg/day. An oral form should supplant the injectable form as soon as possible. It may be necessary to adjust the dosage when changing from the intramuscular to oral dosage forms Dosage recommendations for Navane (thiothixene) Capsules and Concentrate appear in the following paragraphs.

Navane Capsules: Navane Concentrate – In milder conditions, an initial dose of 2 mg three times daily. If indicated, a subsequent increase to 15 mg/day total daily dose is often effective

In more severe conditions, an initial dose of 5 mg twice daily

The usual optimal dose is 20 to 30 mg daily If indicated, an increase to 60 mg/day total daily dose is often effective. Exceeding a total daily dose of 60 mg rarely increases the beneficial response

Overdosage: Manifestations include muscular twitching, drowsiness, and dizziness. Symptoms of gross overdosage may include CNS depression, rigidity, weakness, torticollis, tremor, salivation, dysphagia, hypotension, disturbances of gait, or coma

Treatment: Essentially is symptomatic and supportive For Navane oral, early gastric lavage is helpful For Navane oral and Intramuscular, keep patient under careful observation and maintain an open airway, since involvement of the extrapyramidal system may produce dysphagia and respiratory difficulty in severe overdosage, If hypotension occurs, the standard measures for managing circulatory shock should be used (I.V. fluids and/or vasoconstrictors.)

If a vasoconstrictor is needed, levarterenol and phenylephrine are the most suitable drugs. Other pressor agents, including epinephrine, are not recommended, since phenothiazine derivatives may reverse the usual pressor action of these agents and cause further lowering of the blood pressure.

If CNS depression is present and specific therapy is indicated, recommended stimulants include amphetamine, dextroamphetamine, or caffeine and sodium benzoate Stimulants that may cause convulsions (e.g picrotoxin or pentylenetetrazol) should be avoided Extrapyramidal symptoms may be treated with antiparkinson drugs

There are no data on the use of peritoneal or hemodialysis, but they are known to be of little value in phenothiazine intoxication

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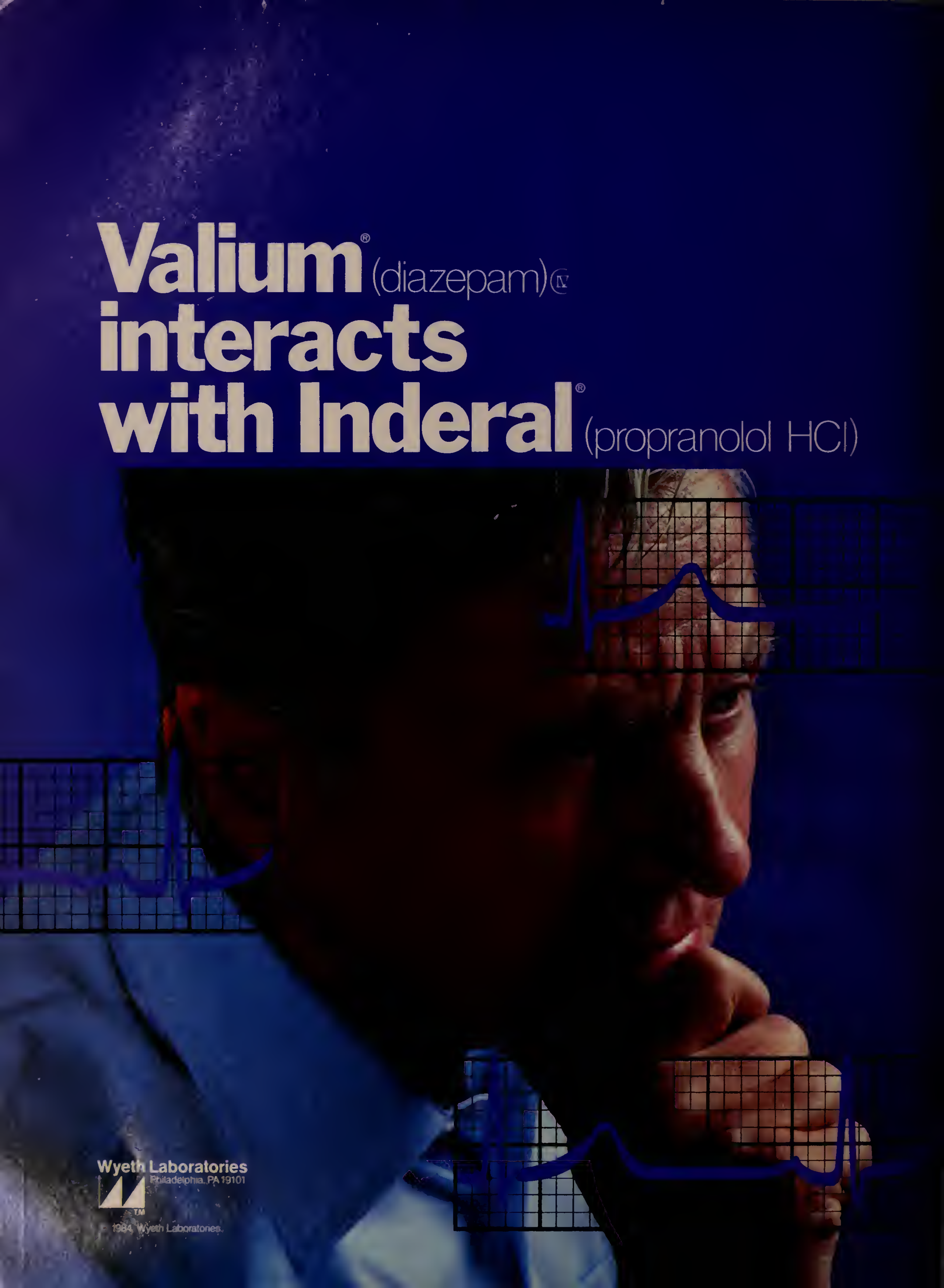

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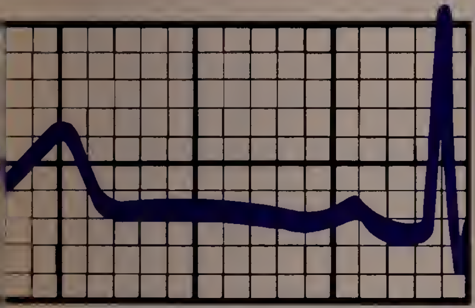

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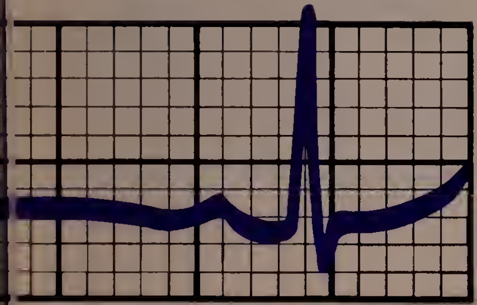

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See important information on following page.

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DISTINCTIVE DESIGN 0.5, 1.0 and 2.0 mg

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated. anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1 25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS· Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed

PREGNANCY· Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4 2%) and unsteadiness (3 4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S P Usefulness of dialysis has not been determined

Ativan® Ⓒ IV for (lorazepam) Anxiety

DOSAGE: Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.

HOW SUPPLIED: 0.5, 1.0 and 2.0mg tablets.

Wyeth Laboratories
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MEETINGS AND LECTURES

MARCH 1984

AROUND THE STATE

MANHATTAN

Mar 1. **Cancer Emergencies: Control of Life-Threatening Complications.** $1\frac{1}{2}$ Cat 1 credits. Info: Clifford L Spingarn, MD, Chairman, Committee on CME, Doctors Hospital, 170 East End Ave, New York, NY 10028. Tel: (212) 870-9000.

Mar 1–2. **Gastrointestinal Oncology.** 16 Cat 1 credits. Info: Ms Charlene Landis, CME Conference Planner, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10021. Tel: (212) 794-6754.

Mar 6, 13, 20, 27, Apr 3. **Hypnosis for Physicians and Dentists.** $7\frac{1}{2}$ Cat 1 credits. *Mar 9–10.* **An Update in the Internal Medicine for Practicing Psychiatrists and Neurologists.** 6 Cat 1 credits. *Mar 21.* **Learning Disability: Treatment in the Real World.** 6 Cat 1 credits. *Mar 26–30.* **Temporal Bone Surgery.** 40 Cat 1 credits. Info: The Page and William Black Postgraduate School of Medicine of the Mount Sinai School of Medicine, One Gustave Levy Pl, New York, NY 10029. Tel: (212) 650-6546.

Mar. 7. **Spinal Cord Injury: Old Problems, New Approaches.** Info: Wanda Brodzka MD, The New York Society of Physical Medicine and Rehabilitation, 103 St and Fifth Ave, New York, NY 10028. Tel: (212) 491-8357.

Mar 10. **Measuring the Disordered Mind: Tools and Strategies from the Cognitive Sciences.** Info: Mitchell Kietzman PHD, Dept of Psychophysiology New York Psychiatric Institute, 722 W 168 St, New York, NY 10032. Tel: (212) 960-2472.

Mar 12. **Pathogenesis of Chronic Renal Disease: Ability to Function in a Work Setting.** *Mar 26.* **Anatomy of Coronary Arteries: Standard Terminology, Anomalies.** Info: Harry R Pace, MD Chief Medical Consultant, New York State Department of Social Services,

(continued on page 12A)

NEW YORK STATE
JOURNAL OF MEDICINE

February 1984 • Volume 84, Number 2

COMMENTARIES

Lung transplantation: problems and progress

Since the development of techniques of vascular anastomosis and experimental organ transplantation by Guthrie reported in 1907,[1] the hope of replacing diseased organs with transplants has fascinated the medical profession. While kidney, heart, and liver transplants have been successful, lung transplantation has proved extremely difficult in experimental animals, and attempts at transplantation in man have produced no long-term survivors.

It may be that the lung is a particularly antigenic organ raising host defenses that result in rejection of the transplant. The lung is also a target organ for infectious agents in all patients who undergo a transplantation procedure, a problem intensified when one of the lungs is the transplanted organ. Because removal of a lung would place an enormous burden on a living donor the cadaver remains the only source for such organs. Ischemic damage of the donor organ is another obstacle to the use of this organ for transplantation. Thus, the surgeon attempting allogeneic nonfamilial transplants confronts problems of infection, ischemia, resistance to graft acceptance, and poor healing of the bronchial anastomosis.

The report in this issue of the *New York State Journal of Medicine* by Kamholz, Veith, et al is evidence of progress in obtaining long-term functioning lung transplants in patients. These investigators have shown cyclosporin A, an agent that can control rejection without excessive complications, can be used for transplantation of the lung in man. They transplanted a lung to a patient with paraquat poisoning, a problem usually affecting both lungs. Although charcoal dialysis was used to remove the chemical, the nontransplanted lung was so damaged by paraquat that contralateral pneumonectomy was required. Complications of the closure of the pneumonectomy bronchus led to a fistula and death of the patient. However, it is encouraging that the anastomosis of the transplanted lung healed without complication.

Recent progress in combined heart and lung transplantation by Reitz and Shumway and their associates has been encouraging.[2] The early experience in heart and lung transplantation has demonstrated a much better early survival rate than unilateral lung transplantation. While heart and lung transplantation may appear extreme, the operative procedure, which involves extracorporeal support and a high degree of technical skill, can be successful. Indeed, this approach has produced more long-term survivors than have the 39 attempts at unilateral or bilateral transplantation of the lung alone. For the moment, it would appear that combined heart and lung transplantation is a more effective form of therapy for end-stage pulmonary disease, particularly for those problems complicated by end-stage pulmonary hypertension, than is transplantation of the lung alone.

A major problem for both lung transplantation and combined heart and lung transplantation remains effective preservation of the lung *in vitro*. While hearts and kidneys can be preserved as isolated organs and transported long distances, the donor of a lung or combined heart and lung transplant must be present in the operating room adjacent to the recipient to ensure a viable transplant. Improved methods of preserving the lung are a high priority for investigation. The ultimate solution to treatment of patients with end-stage pulmonary disease lies in clarifying the etiology and preventing the disease process. In many diseases, such as emphysema, carcinoma, and toxic pneumonitis, the causative agents have been identified and it remains for us to apply preventive measures to eliminate these diseases. Until such time as the medical profession and society at large are willing to implement such preventive measures, transplantation may remain the only effective therapy for many forms of end-stage pulmonary disease.

DAVID A. BLUMENSTOCK, MD
Professor of Clinical Surgery
The Mary Imogene Bassett Hospital
Cooperstown, New York 13326

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Single lung transplantation

Drs Kamholz, Veith, and colleagues are to be congratulated for their perseverance in the field of single lung transplantation. While these and other investigators have shown that short-term survival following single lung transplantation is possible, long-term prospects remain dim. While cyclosporine is a powerful immune suppressant, it will not in and of itself make single lung transplantation a commonly performed and highly successful operation. Although the use of cyclosporine enables steroid coverage to be withheld for the first two to three weeks following transplantation, and technical advances such as the use of omental flaps and distally placed anastomoses limit the potential for bronchial disruption, the major obstacle facing the success of single lung transplantation is the proper selection of candidates. Recent clinical failures of this operation have resulted, in one way or another, from the fact that the nontransplanted opposite lung remains diseased.

Although Drs Kamholz and Veith have demonstrated that paraquat can be removed from muscle and blood using charcoal hemofiltration, their patient died presumably because the nontransplanted lung, damaged by the paraquat insecticide, became a reservoir for a morbid *Pseudomonas* pneumonia. The clinical carousel of treatment for infection and rejection was begun, and the usual result obtained. A similar case of paraquat poisoning was recently treated by Joel Cooper, MD at the Toronto General Hospital; unilateral lung transplantation was successful, but the contralateral lung became damaged by residual paraquat and infection. It, too, required excision and a contralateral transplant was performed. The bilateral lung implants became increasingly functional with time, and bronchial anastomoses healed with the benefit of combined omental and pericardial flaps. This patient required three weeks of extracorporeal membrane oxygenation to support him during his healing phase. What was a successful and daring surgical procedure ultimately failed, as the patient died due to paraquat induced disease and renal failure.

It would appear that if all diseased pulmonary tissue can be removed at a single procedure, some advantage may be served. This can be accomplished by bilateral single lung transplantation, but perhaps more simply by combined heart and lung transplantation. The latter technique avoids bilateral bronchial anastomoses and has recently been associated with minimal tracheal anastomotic problems. Nine patients of 12 at Stanford, and four patients of six at the University of Pittsburgh have survived combined heart and lung transplantation. The patients who have undergone successful transplantation had been ideal candidates in that they have led New York Association Class IV existences and have not required transplantation in the shadow of acute pneumonia or cardiovascular decompensation. Twelve of the 13 survivors have had some form of pulmonary vascular disease. The remaining survivor was treated in Pittsburgh for chronic obstructive lung disease. The success in this patient suggests that combined heart-lung transplantation may be beneficial for patients with obstructive lung disease.

Single lung transplantation for pulmonary vascular disease is likely to fail as it will not be performed until there is evidence of cor pulmonale, and the acute perioperative cardiovascular requirements will not likely be supported. The unlikelihood of success has been borne out as a patient in Toronto with pulmonary vascular disease and cor pulmonale died of nonreversed right ventricular failure the day after single lung transplantation. Most lung transplant surgeons also agree that obligatory postoperative ventilation perfusion imbalances make patients with end-stage obstructive diseases poor candidates. As the authors have shown, it would appear that refinements in surgical techniques and the use of cyclosporine can guarantee early successes, but that recipients with acute illnesses are unlikely to survive. A survey of lung disorders acceptable for treatment suggests a more fruitful area in single lung transplantation may be in those with fibrotic lung diseases without infection, chronic obstructive pulmonary disease, or significant cor pulmonale.

BARTLEY P. GRIFFITH, MD
Assistant Professor of Surgery
University of Pittsburgh School of Medicine
Pittsburgh, PA 15621

Anorexia nervosa and juvenile diabetes mellitus

The case reported by Hardoff et al in this issue of the *Journal* is a timely one. It should stimulate the reporting of similar cases, as happened in England after Fairburn and Steel[1] in 1980 published a short report in the *British Medical Journal* of three cases of insulin dependent diabetes (in patients aged 11, 13, and 17 years) who subsequently developed anorexia nervosa with severe weight loss. The status of the diabetes was only briefly mentioned, but ketoacidosis and hypoglycemia did not create a problem in these cases.

Soon after this report Gomez et al[2] related their experience with two patients: one was diagnosed as having diabetes at the age of 13 years; she developed ketoacidosis four years later but was easily managed. The other patient whose diabetes was first diagnosed at the age of nine years manifested anorexia nervosa at the age of 14½ years. This girl had a stormy course with recurring severe hypoglycemia; she eventually had seizures and was found dead in bed shortly thereafter.

Garner[3] reported the clinical course of a 20-year-old woman who had insulin-dependent diabetes since the age of 13½ years. Three years after the onset, she became anorectic and had frequent epidoses of ketonuria because she reduced her dosage of insulin to control her weight. Two years later she required phenytoin for noctural seizures. Her subsequent course during the period of anorexia nervosa included ketoacidosis five times and frequent hypoglycemic episodes.

Adin and Nelkin[4] relate the case of a girl whose diabetes was diagnosed at the age of 11 years and who was a noncompliant patient. She developed anorexia nervosa at the age of 15 years and yet had constant glycosuria and repeated episodes of ketonuria. She developed diabetic retinopathy with blindness seven years after the diabetes was discovered; starvation did not prevent the blindness.

All but one of the above reports were submitted by psychiatrically oriented physicians who had no special training in the endocrinologic complexities of diabetes mellitus. Yet such cases can teach us much concerning the nature and perhaps the etiology of juvenile diabetes. The response of the different patients to starvation and then refeeding emphasizes the heterogenous etiology of juvenile diabetes. The combination of juvenile diabetes and anorexia nervosa is a natural experiment; a study of the response of diabetes to starvation might help to identify different endocrine patterns and prolong life for the individual patient.

More recently two additional papers concerning patients with anorexia nervosa and type I diabetes have been published.[5,6] Of a total of seven cases reported, only four had episodes of ketoacidosis and two presented evidence of retinopathy. One patient developed exocrine pancreatic deficiency.

It must be remembered that starvation was a modality of treatment before the discovery of insulin and it lengthened the life—albeit a miserable one—for certain juvenile patients. The present report by Hardoff et al has included for the first time significant information relative to the diabetes. The C-peptide estimation demonstrated the patient's residual ability to secrete insulin. This could explain why insulin therapy could be discontinued during starvation periods without creating ketoacidosis.

In a recent textbook on diabetes mellitus by Ellenberg and Rifkin[7] the heterogeneous etiology of insulin-dependent diabetes mellitus (IDDM) is emphasized; using vast immunologic information collected in recent years, the authors attempt a classification. One group of juvenile patients with positive antigen typing HLA-B8, Dw3 have autoimmune antibodies against the pancreas for years and develop IDDM at a relatively later age. These patients also have antibodies against other endocrine glands which complicates treatment. In another group of patients the HLA-B15, Dw4 antigen is virally induced. They have transient antibodies against the pancreas which disappear in about a year, and they also have increased antibodies to insulin at an early age. A third group consists of young children who have combined features. Such a classification is in a state of flux as demonstrated recently at an American Diabetes Association symposium chaired by Harold Lebovitz, MD of SUNY in Brooklyn.[8] Sufficient immunologic data have been collected to allow attempts to prevent IDDM by suppression of the antibodies.

Last, there is the group of young patients with diabetes who have the maturity onset type of diabetes occurring in slightly older youngsters (the MODY of Tattersall and Fajans).[9] In these cases, starvation clears the diabetes for a while.

It is hoped that the present authors' paper will encourage the reporting of additional cases and that their reports will stimulate research groups to analyze the type of diabetes; a specimen of blood not only would increase knowledge but would help guide the treatment and lead to prognostic precautions.

MILTON B. HANDELSMAN, MD
Honorary Consultant
Deparment of Medicine
Long Island College Hospital
340 Henry Street
Brooklyn, New York 11201

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Retinal hemorrhage, meningitis, and child abuse

The finding of retinal hemorrhage in an infant as reported by Springate in this issue of the *Journal* is uncommon. In neonates it can result from birth trauma during both vaginal (20%) and cesarean delivery (3%).[1,2] Outside the immediate newborn period, the appearance of retinal hemorrhages is considered by many to be of traumatic origin and a reliable indicator of nonaccidental injury. Grabbing the extremities or thorax and shaking the infant causes traction-stretching stresses on the cerebral bridging veins. Intracranial hemorrhage in the form of subdural hematoma may result, and 50% to 70% of these children will also demonstrate retinal hemorrhage.[3] Compression of the thorax may directly increase the intravascular pressure in the head and eyes and result in retinal hemorrhages without associated subdural hematomas.[4] This Purtscher retinopathy has also been described in patients wearing shoulder harnesses during minor traffic accidents. For years, the traumatic origin of these injuries went undiscovered due to the absence of other signs of trauma. That such injuries do occur has been documented by Caffey.[5,6]

The diagnosis of subdural hematoma requires a high index of suspicion. The nonspecific findings of irritability, vomiting, and fever may mistakenly lead to an impression of infection as with the present case. When retinal hemorrhage is present, the investigation for intracranial hemorrhage must be vigorous.

Despite assertions to the contrary, it is often impossible to make the diagnosis of child abuse and neglect with any degree of certainty. In the absence of such certainty, however, we cannot abandon our patients and their families. In our work we have found a supportive, nonjudgmental approach to be helpful. These problems are, after all, symptoms, not diseases which present themselves for simplistic cures. The existence of the symptom is reason enough to form a helping alliance between the families and the professionals and lead to the provision of comprehensive service plans for both child and family. The familiar model of identifying (labeling) and reporting (punishing) must be discarded as inadequate. The report alone does not provide the long-term help and protection necessary. The major function of the Protective Service System is the coordination and provision of acute care services. Effective long-term management involves the coordinated efforts of several disciplines.

Pediatricians are among the few professionals who are likely to maintain contact with a family after other treatment services are terminated.[7] They can prevent the gaps in services that may occur when many disciplines are involved. If the aforementioned alliance is formed, these services provided by physicians, nurses, social workers, and courts can be utilized more effectively.[8] In these situations, as at other times, our patients and their families deserve our best. No one should expect any less.[9]

DANIEL B. KESSLER, MD
Chief
FRANCINE SIEGEL-STEIN, MD
Fellow
Division of Child Development
The New York Hospital
525 East 68th St
New York, NY 10021

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MORE CHILD ABUSE

In the month following publication of the December issue on the world cigarette pandemic, the *Journal* has received nearly 100 letters as well as orders for more than 2000 copies. A selection of readers' comments will appear in a forthcoming issue.

Meanwhile it is important to point out several current preventable examples of the advertising assault by tobacco companies on young people—an exploitation yet to be addressed by the mass media in New York. To the contrary, the press appear to acquiesce in the promotion of cigarettes through sport. From February 28 to March 4, Philip Morris' Virginia Slims Cigarettes tennis tournament will run (wheeze?) at Madison Square Garden. Last year's advertisements for this cigarette promotion (featuring players as young as 14) were broadcast on several radio stations, including WCBS, in violation of the Public Health Cigarette Smoking Act. The cigarette brand received countless mentions on sports broadcasts and in newspaper articles, as well as live television exposure on a cable channel. Although cigarette advertising was banned from television by Congress in 1970 as a means of protecting children, cigarette promotions masquerading as sports events now make a mockery of the athletes—and the law.

Another sick trend is the televising of such suicidal pseudosports as motocross and drag racing, events which reap a rich harvest for cigarette sponsor R. J. Reynolds. And the audience is young indeed. At 8 a m one Saturday last June, children who settled down to watch "Bullwinkle" on WNEW-TV were treated instead to the Winston Cajun Nationals Drag Racing championships, co-sponsored by Annheuser-Busch's Budweiser Beer. Several hundred pictures of Winston cigarette signs and Budweiser logos were shown throughout this one-hour spectacle. CBS-TV continues to televise similar cigarette-sponsored events year-round. Small wonder why a recent CBS "Sixty Minutes" program tried to make light of the efforts of those who are waging legislative battles for the right to breath clean air. (In their zeal to condemn the non-smoking zealots, the news media never seem to acknowledge the right of children to a smoke-free environment.) Also not noted was the annual income of at least $100 million that CBS derives from tobacco companies, in the form of advertising in its publications (including *Woman's Day*, *Field and Stream*, *Cycle World*, *Road & Track*, *Family Weekly*, *Mechanix Illustrated*, *Cuisine*, and *World Tennis*) as well as for such tobacco company products as Miller Beer.

Although high-speed driving has been cultivated as the social norm in automobile commercials and on such programs as "The Dukes of Hazard," Atari and R. J. Reynolds appear to have gone one step better by featuring miniature billboards for Winston cigarettes in the popular children's video arcade game, "Pole Position." The United States Tobacco Company, whose snuff product is being advertised on television this year in association with coverage of the Olympic Games, is another principal sponsor of auto racing and motocross and sends automobiles roaming around New York painted with the Skoal racing logos.

This year in a series of newspaper and magazine advertisements that violate the company's own agreement with the Federal Trade Commission to include the requisite warning about the dangers of cigarette smoking, R. J. Reynolds is attempting to make the public believe it has no interest in encouraging young people to smoke. Although it spends $500 million on cigarette advertising each year, it cannot imagine how a few hundred thousand advertisements at sports stadiums, rock concerts, street fairs, and on more than 2000 items from beach towels to t-shirts could influence a single child to go "Where a man belongs" and light up a Camel.

"Can we have an open debate about smoking?" these sociopathic ads demand.

What is rather more needed is Congressional investigation into the willful undermining of public health by tobacco companies

ALAN BLUM, MD

LETTERS TO THE EDITOR

Address correspondence to Editor, New York State Journal of Medicine, *420 Lakeville Road, Lake Success, NY 11042. Letters should be typed double-spaced and include the signature, academic degree, professional affiliation, and address of each author. Preference is given to letters not exceeding 450 words, and every effort will be made to assure prompt publication. All letters are personally acknowledged by the Editor.*

Anorexia nervosa in a patient with juvenile diabetes

TO THE EDITOR: We would like to report an unusual patient who has both diabetes mellitus and anorexia nervosa. In searching the literature, we have found reports of eight patients with this association. We recently had the opportunity of treating two such patients. Of particular interest is that one of these patients did not require insulin treatment for two periods of up to two months duration.

Case report. The patient was first diagnosed as having diabetes mellitus at age 14½, when she was seen at another institution in diabetic ketoacidosis. Her initial insulin requirements were 30 units of lente insulin per day, and she did not appear to have any major adjustment problems to her disease. Her father also had had diabetes mellitus, and he had died suddenly from a myocardial infarction when the patient was seven years of age. A maternal grandmother also suffered from diabetes. One and a half years after the onset of the patient's diabetes her grandmother died. At that time the patient became preoccupied with her weight. She ate little and increased her physical activity. She became more withdrawn and isolated from her peers. In eight months her weight decreased from 90 lb to 70 lb and she became amenorrheic. During this time, her insulin requirements gradually decreased to 14 units per day. At 70 lb of weight the patient was hospitalized at another institution and her blood glucose was between 75 and 150 mg/dL. She no longer required insulin. As the patient's weight increased from 70 to 75 lb she required raised insulin doses to control hyperglycemia. Her initial hospitalization for anorexia was 70 days in duration and at the time of discharge she weighed 80 lb. However, her eating habits did not substantially improve and she gradually began to lose weight once again. We initially saw this patient six weeks following a hospital discharge at which time she weighed 69 lb and did not require insulin to control hyperglycemia. She appeared severely malnourished, and was withdrawn but cooperative. Physical examination was otherwise unremarkable. Her height was 63 inches. Her urine was negative for glucose and acetone. The blood glucose level was 147 mg/dL. Other values were BUN, 22 mg/dL; sodium 140 mEq/L; potassium, 3.7 mEq/L; chloride, 101 mEq/L; CO_2 30 mEq/L, total serum protein, 6.9 mg/dL. Erythrocyte sedimentation rate was 10 mm/hr (Westegren).

A vigorous program of behavior modification therapy was begun. The patient received an 1,800 calorie diet. She was compliant with this regime and gained weight continuously, while gradually increasing caloric intake up to 2,800 calories per day. For the first 17 days of this hospitalization the patient did not require insulin. Her blood glucose levels ranged between 105 and 150 mg/dL, both fasting and postprandial. Her fasting C-peptide levels were below 0.5 ng/dL and the postprandial C-peptide levels were 2.0 ng/dL. The hemoglobin A_1C was 6.6%. On the 18th day of hospitalization the patient weighed 77 lb and her urine was noted to contain glucose. Her blood glucose level was 350 mg/dL. Since that time and with continued weight gain, the patient has required insulin supplements daily. Upon discharge, after two months of hospitalization the patient's weight stabilized at 94 lb and her insulin requirements were maintained at about 30 units per day.

Discussion. Although the transient reduction of insulin requirements in patients newly diagnosed as having diabetes mellitus is a well known phenomenon (the "honeymoon phase"), prolonged lack of insulin requirements in a patient with known diabetes who has developed anorexia nervosa may not have been previously recorded. This patient represents a natural experiment in starvation therapy, a treatment approach used in the management of diabetes mellitus prior to the discovery of insulin. Type 1 diabetic patients have been shown to have residual function of up to ten years of their beta cells after the onset of the disease. The more stable the diabetes, the higher the residual C-peptide concentrations. Patients with anorexia nervosa have been shown to have an increased binding of insulin to erythrocytes and to monocytes. This phenomenon has been shown to disappear when the anorexic patients improve their nutritional status. In this patient 75 pounds appeared to be a critical weight for the requirement of insulin supplementation. The residual C-peptide concentrations that were demonstrated indicated that there were sufficient levels to maintain normal glycemia in her emaciated state, probably because of an increased sensitivity to insulin secondary to severe malnutrition. Once the critical weight was reached, the sensitivity to insulin presumably diminished resulting in increased levels of blood glucose and exogenous insulin requirements. This case also illustrates a combination of two illnesses in which a different dietary approach could be utilized to control one disease while aggravating the other. As anorexia nervosa appears to be increasing in incidence, it seems likely that this combination of circumstances may occur again in other patients.

DANIEL HARDOFF, MD
I. RONALD SHENKER, MD
MICHAEL NUSSBAUM, MD
Department of Pediatrics
Long Island Jewish-Hillside
Medical Center
New Hyde Park, NY 10042

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Retinal hemorrhage in an infant after recovery from meningitis

TO THE EDITOR: Relapse of bacterial meningitis is an uncommon but well-defined entity.[1] Originally felt to be such a relapse, the following case took a surprising turn of events.

Case report. A 9-month-old girl was brought to the emergency room by her mother with a two-day history of fever, irritability and vomiting. She had been discharged from another hospital seven days earlier after completing a ten-day course of intravenous ampicillin for *Hemophilus influenzae* meningitis without complication. One day earlier, she had been seen at another hospital for similar complaints and placed on clear fluids for presumed gastroenteritis. Her birth and past medical history were otherwise unremarkable. Her mother was unmarried and lived alone.

Upon examination, the infant was well-developed and nourished but lethargic, responding only to pain or vigorous stimulation. Her temperature was 38.5°C rectally; her pulse 84; blood pressure 110/60, and respiratory rate 30. Her weight and height were in the 25th percentile for age, her head circumference 75th percentile for age. Her skin and skeleton were normal. There were no meningeal signs. Her fontanel was slightly full; the sutures were normal. There were no abnormalities of her eyes, ears, nose, or pharynx. The chest was clear and the cardiovascular system normal, as were her abdomen and genitalia. There were no focal neurologic signs. Complete blood count, serum electrolytes, coagulation profile, and urinalysis were all within normal limits.

Thirty minutes later, her pulse was 66 and blood pressure 115/75. Funduscopic examination revealed multiple retinal hemorrhages without evidence of papilledema or retinal detachment. Skull radiographs disclosed a 4-cm nondepressed linear fracture of the right parietal bone. Emergency CT scan of the head was consistent with a subdural fluid collection overlying the frontal lobes. Bilateral subdural hematomas were evacuated with good result. Appropriate investigation for possible child abuse was instituted, but remains inconclusive at present.

Discussion. The relapse rate following appropriate therapy for *H. influenzae* meningitis with ampicillin is approximately 4%.[2] Recurrence has been documented at any time between one day and two weeks after completion of therapy.[3] This infant presented with a two-day history compatible with such a relapse. However, her decreasing level of consciousness, bradycardia, and hypertension pointed to an acute increase in intracranial pressure possibly from postmeningitic hydrocephalus, effusion, or brain abscess. Prior to the originally planned lumbar puncture, a funduscopic examination was done with the unexpected discovery of retinal hemorrhages. Although retinal hemorrhage may accompany any abrupt increase in intracranial pressure, their appearance is said to be so characteristic of abusive head injury that skull radiographs were obtained while awaiting the CT scan.[4]

Sadly, child abuse remains an important consideration in pediatric differential diagnosis. According to McNeese and Hebeler,[5] prerequisites for abuse include (1) a child who is perceived as difficult to manage, (2) a parent with the potential to abuse, and (3) a series of stressful events that antedate the abuse. Although the exact circumstances surrounding this infant's injury are not known, it is possible that recurrent illness or other factors coupled with stress induced by prior hospitalization were involved. Early identification of potentially abusive families of patients admitted to the hospital, followed by appropriate supportive counseling, anticipatory guidance, and continuity of care may avert such tragic situations.

JAMES E. SPRINGATE, MD
Department of Pediatrics
The Children's Hospital of Buffalo
219 Bryant St
Buffalo, NY 14222

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The epidemiology and control of Rocky Mountain spotted fever

TO THE EDITOR: I wish to elaborate on the Commentary on tick-borne diseases by Richard B. Hornick, MD (*NY State J Med* 1983; 83:1036) and share our experience with Rocky Mountain spotted fever in Suffolk County, the recognized endemic focus for the disease in New York State.

The diagnosis of Rocky Mountain spotted fever depends on a history of tick bite and the presence of the characteristic rash and positive laboratory findings. The latter include the Weil-Felix reaction and specific complement fixation, rickettsial agglutination and neutralization tests. Aggulutinins for bacillus *Proteus OX-19* and *OX-2* appear during the second week of illness and last for several weeks. The more specific agglutinins appear during the second or third week and last for several months. A titer of 1:160 for the Weil-Felix reaction or 1:10 for the complement fixation test are considered indicative of infection.

Because of the vague symptoms in the prodromal period, the disease may simulate upper respiratory and other nonspecific infections. Physicians treating patients with vague symptoms in endemic areas during the tick season should get a detailed history of contact with ticks. Unfortunately, the prescription of antibiotics in misdiagnosed cases often aborts the full development of the rash and delays the emergence of agglutinins. A presumptive diagnosis based on the clinical findings and on contact with ticks should justify the administration of tetracycline, the most effective antibiotic for treating Rocky Mountain spotted fever.

For confirming the diagnosis, serologic testing should be performed during the first few days of illness, during the second week and four to six weeks after onset.

The prevalence of infection in the tick population varies greatly between one infested area and another and between the different seasons. In our experience in Suffolk County, infection rates among tick populations far exceed the 0.1% to 0.2% mentioned in the commentary. Examination of tick samples revealed the presence of *Rickettsia rickettsii* in 11% of the ticks examined.

At present the control of Rocky Mountain spotted fever depends on the promotion of community education and on alerting the medical profession to the problem. In recommending preventive measures one has to be realistic in order to ensure implementation. To recommend avoidance of tick-infested areas may be impossible in many residential and recreational areas.

Because Rocky Mountain spotted fever in the Northeast occurs most frequently in children and young adults, it is of utmost importance that children be properly dressed. They should preferably wear bright, solid colored tucked in pants and boots. In this way, ticks can more easily be identified and removed. Pets should be inspected frequently and, if infested, should be shampooed or dusted with an appropriate insecticide powder.

Fingers should never be used for removing ticks from human or animal hosts because infection can be transmitted during the process. Grasp the tick firmly with a pair of tweezers at the point where its mouth parts penetrate the skin and pull gently outward while moving the tick back and forth. The application of a drop of mineral oil or vaseline can help in removal because this suffocates the attached tick.

Area control—the application of pesticides to heavily infested areas—has been tried on a limited scale in Suffolk County. However, this type of control is neither effective nor desirable. It is practically impossible to kill the tick population, whether in its adult form or nymphal stage on domestic animals and rodents, through the mass application of pesticides. In addition, there is always the added risk of groundwater contamination with pesticides.

To summarize, the physician has a dual responsibility with regard to Rocky Mountain spotted fever. The first is to make a tentative diagnosis in the absence of the classical rash and usual clinical picture and to initiate tetracycline therapy, and the second is to educate patients in preventive measures.

MAHFOUZ H. ZAKI, MD, DR PH
Director of Public Health, Suffolk County
Hauppauge, NY 11787

Hemophilus parainfluenzae bacteremia in children

TO THE EDITOR: In the past 15 years a number of serious infections due to *Hemophilus parainfluenzae* have been reported in the pediatric and medical literature.[1-5] Meningitis, septicemia, epiglottitis, endocarditis, and pneumonia have all been described. However, to the best of our knowledge only a few cases of bacteremia due to *H. parainfluenzae* have been reported in children. We wish to present two cases of bacteremia due to *H. parainfluenzae* with no localization and rapid response to therapy.

Case 1. A 7-month-old girl had fever, irritability, and poor feeding of one day's duration. She had no cold, cough, diarrhea, or vomiting. Past history was unremarkable. On physical examination the infant was irritable, with a temperature of 38.8°C (102°F), heart rate of 160/min, respiratory rate of 50/min, and weight of 16 lb, 8 oz. There was no respiratory distress and the anterior fontanel was normal. There were no meningeal signs. Examination of the head, eyes, ears, nose, throat, extremities and joints disclosed no abnormalities. The patient was admitted to the hospital to rule out sepsis. Complete blood count showed WBC 23,800/mm^3, neutrophils 64%, band forms 20%, lymphocytes 10%, monocytes 5%, eosinophils 1%; hemoglobin was 12.8 g/dL; platelet count, 266,000/mm^3. Urinalysis was negative except for 20 to 22 WBC per high power field. Spinal tap revealed clear fluid with 2 RBC/mm^3 and no WBC. CSF protein was 27 mg/dL, glucose 16 mg/dL, lactic acid 10.8 mg/dL. Chest x-ray films were normal. After obtaining all cultures, treatment with intravenous ampicillin was started. Within 24 hours, the patient became afebrile and the irritability subsided. At 48 hours cultures of blood, CSF, urine, and throat were negative and the patient was sent home on a regimen of oral amoxicillin. However, the blood culture grew gram-negative rods at 72 hours and the organism was identified as *H. parainfluenzae.* Since the patient was doing well on the oral antibiotic at this time it was continued for 10 days. Repeat blood cultures were negative.

Case 2. A 4-year-old boy had high fever, vomiting, and headache of one day's duration. There was no history of nasal discharge, cough, abdominal pain, or diarrhea. His one-year-old brother was treated for cellulitis of the face a week earlier. Past history was unremarkable. Physical examination revealed an alert but irritable child in no acute distress. His temperature was 39.6°C (103°F), pulse 128/min, respirations, 24/min. The head, eyes, ears, nose, throat, heart, lungs, abdomen, extremities and joints were normal. There was questionable neck stiffness but Kernig's and Brudzinski's signs were negative. Urinalysis was negative. Spinal tap revealed traumatic CSF with 8,000 RBC/mm^3 and 35 WBC/mm^3 (87% polymorphonuclear leukocytes and 13% lymphocytes), CSF protein 67 mg/dL, glucose 75 mg/dL. The increased number of WBC in the CSF is consistent with the traumatic nature of the fluid and the leukocytosis of the peripheral blood. After appropriate cultures were obtained, the patient was started on intravenous ampicillin. He became afebrile within 48 hours and was discharged home the third day on a regimen of amoxicillin, because blood, CSF, and urine cultures were negative at 48 hours. His blood culture, however, grew gram-negative rods at 72 hours; these were identified as *Hemophilus parainfluenza* sensitive to all antibiotics including penicillin, ampicillin, trimethoprim, and sulfamethoxazole. Blood culture repeated on the fourth day was negative and the patient continued to do well on oral amoxicillin for 10 days.

Discussion. Hemophilus parainfluenzae is a small, fastidious gram-negative rod that is morphologically similar to *H. influenzae.* It can be differentiated by its growth requirements of factor V, where as *H. influenzae* requires factors V and X. Occasionally, on subculture from nutrient media like chocolate agar which contains factor X, strains of *H. influenzae* will require factor V alone for growth. Therefore, *H. influenzae* could be mistaken for *H. parainfluenzae.*

H. parainfluenzae is part of the normal flora of the upper respiratory tract, oral cavity, vagina, and small intestines.[6] The two cases of *H. parainfluenzae* bacteremia we are reporting were seen within one month. Hable has previously reported seven cases of meningitis in 16 months and Holt three cases of meningitis in one month.[2] It seems possible, in view of the sporadic identification, that we are dealing with miniepidemics. We submit that the pathogenic potential of different *H. parainfluenzae* organisms is not identical and that some hitherto unexplained epidemiologic circumstance may play a role in the clustering of cases. The two children described in our report are unrelated, had no common exposure, and did not share any identifiable epidemiologic variables. The good outcome in both cases indicates that infections caused by *H. parainfluenzae* may have a wide spectrum of clinical manifestations varying from mild to severe infections, as seen in the disease caused by *Hemophilus influenzae.*

SOMASUNDARAM JAYABOSE, MD
DONALD S. GROMISCH, MD
RAANA AKBAR, MD
Department of Pediatrics

YVONNE LUE, PhD
Department of Pathology
New York Medical College
Lincoln Medical and Mental Health Center
234 East 149th St.
Bronx, NY 10451

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Perforation of the esophagus by a fine feeding tube

TO THE EDITOR: Insertion of feeding tubes to support enteral alimentation is considered to be a minor chore and is often delegated to junior house-officers. However, the insertion and proper placement of a fine-caliber soft feeding tube may be difficult and can be associated with dangerous complications. Commonly recognized problems include coiling of the tube in the pharynx or esophagus and passage of the tube into the larynx and trachea.

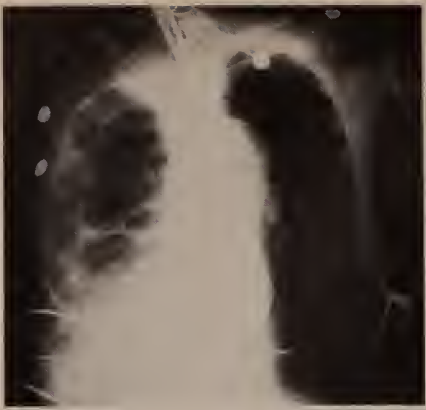
This is a report of an unfortunate case in which a fine feeding tube perforated the esophagus and mediastinal pleura, resulting in hydropneumothorax and death.

Case report. An 84-year-old woman with a long history of chronic obstructive pulmonary disease was admitted to the hospital in acute respiratory failure. She required prolonged ventilatory support on a mechanical ventilator because of her poor general condition and her poor respiratory status. Enteral alimentation was administered through a fine feeding tube. She was doing poorly and could not be weaned from the ventilator.

On the evening of the 46th hospital day, she accidentally pulled out her feeding tube. A house officer reinserted the tube and enteral alimentation was resumed as a slow continuous drip. About six hours after reinsertion of the feeding tube, the patient became restless and hypotensive. A chest x-ray was taken immediately; it revealed a right hydropneumothorax with the feeding tube coiled in the right side of the chest (Fig). A chest tube was inserted immediately and a large amount of milky fluid of the same consistency and physical character as the elemental diet was evacuated from the right side of the chest. The patient went into cardiac arrest and resuscitation attempts were of no avail. A request for autopsy consent was denied.

A chest x-ray taken at the time of cardiac arrest showed the feeding tube to be in the chest cavity outside of the esophagus. The patient had been relatively stable until then and no other cause could be detected for the hydrothorax. It is believed that the sharp metallic stylet exited through the side hole and pushed part of the tube through the esophagus into the pleural cavity.

Discussion. Perforation of the esophagus is known to occur secondary to instrumentation such as bougienage, Mosherbag dilatation, endotracheal intubation, Sengstaken-Blakemore tube, and endoscopy.[1-3] Passage of a soft nasogastric tube is considered to be an innocuous procedure. In order to support prolonged enteral alimentation, a variety of fine tubes have been developed. Each one of them presents a certain technical problem in insertion and care. The feeding tube that was used in this case was a size 8 F 109-cm long Entriflex feeding tube. This is a fine-caliber soft polyurethane tube with a metallic stylet to provide stiffness and a mercury weight at the tip. The tube is passed with the stylet inside, securely positioned against the weighted tip. However, even partial retraction or pulling may cause the wire to exit through the side hole at the distal outlet. The common problems noted are coiling of the tube in the pharynx, difficulty in positioning the tube properly, and passage of the tube into the trachea.[4,5] There have been occasional case reports where a misdirected nasoenteric tube has caused esophageal perforation,[6] gastric perforation,[7] pneumothorax,[8,9] and even penetration to the brain.[10]



Right hydropneumothorax, with feeding tube coiled in right side of chest.

Because of these problems, it has been recommended that feeding should be started only after proper placement of the tube is confirmed, not only by clinical evaluation such as hearing gurgling sounds in the epigastrium after injection of air into the tube or aspirating gastric juice, but also by radiologic confirmation. It is important to follow carefully the instruction manual that accompanies these new products. Periodic reenforcement of the procedures is necessary, because of the frequent turnover of medical and paramedical personnel in large institutions.

VENKIT S. IYER, MD
Assistant Professor of Surgery
J. REICHEL, MD
Department of Medicine
The Hospital of the Albert Einstein
College of Medicine
1825 Eastchester Road
Bronx, NY 10461

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Bernard Straus, MD, 1912–1983

A teacher of medicine

Dr Bernard Straus, who directed the expansion of the department of medicine and clinical training programs at Beth Israel Medical Center during the 1970s, was a superb clinician, researcher, author, and teacher. He will be especially well remembered as an advisor and friend to physicians-in-training. The following are excerpts from two of Dr Straus' medical essays.

DEFUNCT AND DYING DISEASES

Disease and death are blood brothers in a relation in which formerly the first represented a dynamic process and the latter an end point. We have seen in our own time a change in which disease has been characterized increasingly by an end point and death has lost its finality. Even the very definition of death, for which we once had an easy answer, is now a subject of controversy, confusion, and soul-searching. Definition retains its philosophic relevance but not its simplicity, and it has become important for our clinical practice. Our concepts of disease, however, remain dynamic and subject to revision and change. The ebb and flow of specific diseases, which sometimes have a beginning and increasingly have an end, is the subject of this discourse.

This will be no nostalgic threnody to dubious diseases of the ancients. We are concerned here only with diseases which have persisted to modern times, beginning roughly about the turn of the century. Before then too many nondescript and fanciful notions existed concerning a variety of disorders to concern us here. They are of interest, to be sure, but belong among the incunabula of medicine.

What did happen to chlorosis, "the green sickness," for example? The name was due to the greenish-yellow color of the affected girls. The disease was also known as the love sickness because love, presumably unrequited, was believed to be an etiologic factor. Chlorosis had a long life beginning in 1520, when it was described as a disease of virgins, until about 1912 when it virtually disappeared. It was interred with a rather belated obituary by W. M. Fowler in 1936. This disorder was believed to be a primary or "essential" anemia "occurring in young girls due in part to hereditary influences, neurosis, ovarian insufficiency, autointoxication or 'copraemia.' " It was thought to be a result of absorption of poisons—leucomaines and ptomaines—from the large bowel. Alternatively it was ascribed to the wearing of tight corsets. Not too long before its demise, it became clear that the green sickness was an iron-deficiency anemia caused by malnutrition with an inadequate intake of iron aggravated by infections, overwork, and poor sanitary conditions. Sir William Osler was aware that iron depletion was a characteristic feature of the disorder and that iron was a specific in the treatment of this condition. Curiously, he states, "It is a minor matter *how* the iron cures chlorosis. . . . Iron is present in the faeces of chlorotic patients before they are placed on any treatment so that the disease does not result from any deficiency of available iron in the food." Since chlorosis was due to a deficiency of iron, and as this deficiency is not uncommon today, why do not the girls turn green any more? We probably shall never know. . . .

—*Bull N Y Acad Med* 1970; 46:686–706

STUDENT POWER AND MEDICAL SEMINARS

The physician educator is a professional physician but often an amateur teacher. He needs training as a teacher through discussion of teaching methods as well as by experience. He also deserves recognition for his efforts and success as a teacher to provide the necessary incentive for him to devote the time and thought required for this essential task. This will help to make his work not merely a chore but a rewarding and satisfying experience. It has become abundantly manifest that if research productivity is to continue to be the primary determinant of faculty productivity and rewards, the education process will suffer. For a medical school, the making of a doctor should be a product and not a byproduct.

—*J Med Educ* 1971; 46:788–790
(with Magdalena R. Berenyi, MD)

Stinging insect hypersensitivity

Safety and efficacy of venom immunotherapy

James R. Golub, md, Sanford R. Kaplan, md, Armond V. Mascia, md

ABSTRACT **Forty-one patients with a history of anaphylactic reaction to an insect sting were given immunotherapy using a protocol such that maintenance dosage of 100 μg per injection was reached in 15 weekly injections of specific venom. A total of 3,109 injections were given. There were 24 local reactions, and only one patient, on two occasions, experienced mild systemic symptoms not requiring epinephrine. Twelve patients were accidentally re-stung on 17 occasions. No systemic symptoms occurred. Immunotherapy for Hymenoptera sensitivity using a protocol in which maintenance dose is reached in 15 weeks is safe and effective.**

(NY State J Med 1984; 84:66–68)

Introduction

There are at least 20 to 40 deaths from insect stings in the United States each year and it is likely that additional such deaths go unreported.[1,2] Between 0.4% and 0.8% of the US population is allergic to insect stings.[3,4] The incidence is believed to be the same in atopic and nonatopic populations,[4] more common among males and in people under 20 years of age. This possibly reflects greater outdoor exposure.

Lack of clinical efficacy and lack of immunologic response to treatment with extract made from the whole body of the Hymenoptera species has been reported.[5] On the other hand, immunologic response and clinical protection have been demonstrated using specific venom and venom sac extracts.[5,6]

However, an incidence of 15% systemic reactions has been reported using a "rush" technique of immunotherapy,[7] such that a dosage of 100 μg of venom per injection is reached in six weeks.

In addition, it has been stated that slower treatment schedules do not decrease the incidence of large local or systemic reactions and in fact increase the number of reactions.[7] This incidence of systemic reactions seemed unusually high and greater than the incidence of systemic reactions to conventional immunotherapy with other allergens.[8] We therefore report our experience using venom immunotherapy utilizing a protocol requiring 15 weeks to reach maintenance dosage. The incidence of systemic and local reactions was low and the degree of protection high.

Patients and Methods

Patients. All patients had had at least one systemic reaction to a sting of one or more of the following insects: honey bee; wasp; yellow jacket; white faced hornet; and yellow hornet. There were 13 females and 28 males. Twenty-three of 41 (56%) were under 21 years of age. Of the patients treated, 13 (32%) had only dermatologic manifestations (urticaria, angioedema). Fourteen (34%) had a severe reaction manifested by airway obstruction (upper or lower or both). Another 14 (34%) had a life-threatening reaction consisting of one or more of the following: shock; unconsciousness; drop in blood pressure. These 41 patients were selected for treatment out of a total of 92 patients referred to our Center. Another 41 patients had negative skin tests and were therefore not treated. Ten patients had significant positive skin tests but elected not to be treated.

All patients demonstrated positive intradermal skin tests to 1.0 μg/mL or less of at least one venom extract. A positive skin test consisted of at least a 1-cm diameter wheal following an intradermal injection of 0.05 mL of venom extract.

Radioallergosorbant testing (RAST) was done on 38 patients. These tests were performed in the hospital laboratory with material furnished by and according to the standard protocol of Pharmacia Laboratories, Piscataway, New Jersey. The antigens used in the determination were honey bee, white faced hornet, yellow jacket, paper wasp, and yellow hornet. The blood was drawn for these tests on the same date that skin testing was done.

RAST was done to yellow jacket, honey bee, and wasp on 38 patients. Three of these patients also had RAST to yellow hornet and white faced hornet after the antigens became available.

Extracts. All venom preparations used for diagnosis and treatment were obtained from Hollister-Stier Laboratories and were reconstituted and diluted according to standard procedures.

Diagnosis. For diagnostic purposes, anaphylaxis was defined as a history of systemic signs or symptoms distant from the site of the sting. Intradermal skin tests were done starting with 0.001 μg/mL concentration of venom and when negative, increased at tenfold increments to a final testing concentration of 1 μg/mL.

Immunotherapy protocol. Immunotherapy was administered using one to five insect venoms or venom sac extracts per patient based on skin test sensitivity. This standard program consists of 15 weekly subcutaneous injections of increasing amounts of venom or venom sac extract starting with 0.05 μg of venom or venom sac extract or both and ending with 100 μg 15 weeks later (Table). This maintenance dose was then repeated in one week, two weeks, and then at four-week intervals thereafter. Patients who had local reactions consisting of erythema not exceeding 4 cm and induration not exceeding 2 cm were considered to have mild local reactions. Moderate local reactions consisted of erythema not exceeding 10 cm and induration greater than 2 cm and less than 5 cm Severe local reactions consisted of erythema greater than 10 cm and induration greater than 5 cm.

Patients who experienced no local reactions or mild local reactions were continued on protocol as shown in the Table. Patients with moderate local reactions had the prior week's dose repeated. Patients with severe local reactions had their dose reduced to

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From the Departments of Medicine (Drs Golub, Kaplan) and Pediatrics (Dr Mascia), New York Medical College, Westchester County Medical Center, Valhalla, New York.

Address correspondence to Dr Golub, 150 Lockwood Ave, New Rochelle, NY 10801

Venom Immunotherapy Protocol

Dose No.	Volume Administered, mL	Concentration of Vial, $\mu g/mL$	Total Dose Administered, μg
1	0.05	1	0.05
2	0.10	1	0.10
3	0.20	1	0.20
4	0.40	1	0.40
5	0.05	10	0.50
6	0.10	10	1.00
7	0.20	10	2.00
8	0.40	10	4.00
9	0.05	100	5.00
10	0.10	100	10.00
11	0.20	100	20.00
12	0.40	100	40.00
13	0.60	100	60.00
14	0.80	100	80.00
15	1.00	100	100.00

the previous dose administered without local reaction.[9] Some patients, therefore, took longer than 15 weeks to arrive at maintenance dosage.

RESULTS

Skin tests. Of the 41 patients, all of whom had at least one positive skin test, 39 were positive to one or more of the vespids, 20 were positive to Polistes, and four were positive to honey bee. Of the 39 patients who had at least one positive test to vespids, 21 patients were positive to all three (yellow jacket, yellow hornet, white faced hornet), nine were positive to yellow jacket alone, six positive to yellow jacket and white faced hornet, and two positive to yellow jacket and yellow hornet. One of the 39 patients did not react to yellow jacket but was positive to white faced hornet and yellow hornet.

RAST. Of the 41 patients with a positive skin test, 38 had IgE RAST performed. Of these 38 patients, significant positive RAST were obtained in 36. Only two patients had a completely negative RAST. Of the 36 patients with significant positive RAST, 32 were positive to yellow jacket, 21 to wasp, and eight to bee. No further attempt was made to correlate RAST with intradermal skin tests since for 35 patients the RAST antigens were available for only three of the necessary five venoms.

Previously WBE-treated *v* untreated patients. The average number of positive skin tests was calculated for two groups. The first group consisted of those patients previously treated with whole body extract (WBE). The other group consisted of those patients who had not had previous whole body treatment. WBE-treated patients had an average of 3.0 positive skin tests. Previously untreated patients had an average of 2.6 positive skin tests.

Reactions to treatment. A total of 3,109 injections were given during this study. On two occasions, one patient developed systemic symptoms following an injection of venom. On the first occasion a sensation of tightness in the chest developed within one hour of the injection and subsided within another hour. On another occasion, the same patient felt "faint" within minutes of the injection. This sensation also subsided spontaneously but that evening the patient experienced generalized malaise. None of these symptoms required the administration of epinephrine.

Twenty-four local reactions occurred in nine patients. Five mild reactions occurred during the buildup phase and required no change in the protocol. Eight moderate local reactions occurred in the buildup phase and were managed by a repeat of the previous dosage according to our protocol. There were no severe local reactions requiring a reduction in previously administered dosage during buildup. While on maintenance, there were nine mild local reactions and two severe local reactions. The two severe local reactions were managed by a reduction in the succeeding injection but subsequently the dose was again raised to maintenance dosage.[9]

Protection. There were 17 accidental re-stings which occurred in 12 patients. One patient was re-stung on three separate occasions. Three patients were re-stung on two occasions and the remaining eight patients were re-stung once each. No systemic reaction occurred in any of these accidentally re-stung patients.

Of the 12 patients who were re-stung without a systemic reaction two had suffered life-threatening reactions previously, seven had had severe reactions, and three had had dermal reactions.

Four of these re-stings occurred prior to reaching a dose of 50 μg of venom. One re-sting occurred within one month of starting immunotherapy. All other re-stings occurred in patients after they had reached a maintenance dose of 100 μg.

DISCUSSION

Early reports of venom immunotherapy indicated that 15% of patients had systemic reactions to immunotherapy at a rate of 1.6 reactions per 100 injections.[7] Our results indicate a systemic reaction rate of 2.5% of patients and 0.06 reactions per 100 injections; neither of our two systemic reactions required epinephrine.

The difference in reaction rate between our study and the earlier one may be explained on the basis of either the different protocol or by the possibility that patients in the earlier study were more sensitive.

Out of 3,109 injections given, there were 24 local reactions 19 of which were deemed severe enough to either repeat or lower the dose. Our reaction rate both systemic and local was low. Therefore, administering venom immunotherapy using a 15-week protocol is safe.

Our results confirm significant protection for treated patients. Twelve of 41 (34%) were accidentally re-stung, two of these patients twice and one three times. On each of these 17 occasions, the reactions were local and thus they were significantly less than the systemic reaction that caused these patients to seek venom immunotherapy. Therefore, the protection rate was 100% for those re-stung. It is of interest to note that four re-stings occurred prior to the patients having received a dose of 50 μg of venom and in one instance occurred in a patient within a month of initiating therapy. It is possible, of course, that these patients were stung with insects other than those to which they were skin test positive, but the high incidence of yellow jackets and wasps in this area suggests otherwise.

It is clear from evaluating whole body extract studies and the natural history of untreated patients who have had prior systemic reactions to insect stings that some 40% of such patients will not experience systemic reactions on re-sting. This may explain the one patient who had no reaction to a re-sting one month after starting immunotherapy and the three patients who did not have a reaction after having received less than 50 μg of venom.

The protection rate in our study is somewhat higher than that indicated by others.[6] This may reflect the small numbers of patients re-stung in this study, the slower method of immunotherapy (although others have indicated that "rush" immunotherapy is better), or the possibility that patients in this study were less sensitive than those in other studies.

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Sensory evoked potentials in adult-onset progressive spastic paraparesis

MASUD SEYAL, MD, PHD, TIMOTHY A. PEDLEY, MD

ABSTRACT **Sensory evoked potentials were obtained in 45 patients with adult-onset progressive spastic paraparesis and no clinical evidence of disease outside the spinal cord. Abnormalities in somatosensory evoked potentials documented subclinical dysfunction of the dorsal column-lemniscal system in 17 patients. Stimulation of both upper and lower extremities was necessary to maximize the incidence of abnormal findings. Visual evoked potentials were abnormal in 76% of patients with probable multiple sclerosis. Evoked potential studies were normal in patients with motor neuron disease. We conclude that sensory evoked potentials are useful in the evaluation of patients with an undiagnosed progressive myelopathy of late onset.**

(NY State J Med 1984; 84:68–71)

INTRODUCTION

In adults with progressive spastic paraparesis and with no clinical evidence of disease outside the spinal cord, initial diagnostic possibilities commonly include multiple sclerosis, cervical spondylosis, and motor neuron disease. Special circumstances, such as family history, may require considerations of other less common entities.

In this study, we assessed the clinical utility of visual, brainstem auditory, and somatosensory evoked potentials (EPs) in the evaluation of patients with progressive spastic paraparesis. Since EPs can demonstrate sensory pathway dysfunction in the absence of clinical symptoms or signs, they may provide evidence of disseminated or multifocal disease in patients whose clinical findings alone could be explained by a single lesion. EPs are thus useful in helping to identify patients with multiple sclerosis.[1–3] Patients with spondylosis and myelopathy should have normal EP studies or demonstrate abnormalities limited to the somatosensory system consistent with a cervical lesion.[4–7] Patients with motor neuron disease should have normal EPs.

PATIENTS AND METHODS

Patient Population

We reviewed the medical records of all patients admitted to the Neurological Institute of Columbia-Presbyterian Medical Center with adult-onset progressive spastic paraparesis between January 1, 1979 and December 31, 1981. Our operational definition of the syndrome was a chronically evolving upper motor neuron weakness primarily affecting the lower extremities not associated with a major sensory deficit or level. Several patients had sphincter involvement but none had symptoms or signs of disease implicating nervous system involvement outside the spinal cord. Forty-five of 71 patients had EP studies as part of their initial evaluation and constitute the study group. They ranged in age from 22 to 78 years. Twenty-five were male. Symptoms had been present from four months to 20 years at the time of evaluation (mean 5.7 years).

Somatosensory evoked potentials (SEPs) following median nerve stimulation at the wrist were obtained in all patients. In addition, 18 had SEPs recorded following peroneal or posterior tibial nerve stimulation. In most patients, pattern reversal visual evoked potentials (VEPs) and brainstem auditory evoked potentials (BAEPs) were performed as well.

Since the study was not a prospective one, patients were not evaluated uniformly. However, all had x-rays of the cervical spine and cerebrospinal fluid (CSF) studies which included measurement of immunoglobulin G (IgG) and agar gel electrophoresis for the identification of oligoclonal bands. Forty-three (96%) had a myelogram. Twenty-seven patients (59%) had electromyographic (EMG) studies and determination of peripheral nerve conduction velocities.

A diagnosis of cervical spondylosis was made if the myelogram showed complete or near-complete (80%) block. Three of these patients subsequently had a decompressive laminectomy. A diagnosis of motor neuron disease was made if EMG studies demonstrated denervation, and the nerve conduction velocities, myelogram, and CSF examination were normal. Probable multiple sclerosis was the diagnosis in those patients who had a normal myelogram and EMG but demonstrated oligoclonal bands or elevated gamma globulin (>13% of total protein) in the CSF without other explanation (eg, negative serologic tests for syphilis, normal serum protein electrophoresis). Eight patients had

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From the Department of Neurology, Columbia University College of Physicians and Surgeons, New York City

Address correspondence to Dr Pedley, Professor of Neurology, The Neurological Institute, 710 W. 168 St, New York, NY 10032.

Dr Seyal is now in the Department of Neurology, University of California Davis Medical Center, Sacramento, CA 95917.

other diagnoses based on family history and the results of additional laboratory testing. Thirteen patients were discharged without a diagnosis.

Techniques of Stimulation and Recording

Somatosensory evoked potentials. Pairs of stimulating electrodes were placed over the median nerve at the wrist and over either the posterior tibial nerve just posterior to the medial malleolus or the peroneal nerve at the knee. The cathode was located 3 cm proximal to the anode. Stimuli (0.2 msec constant voltage square wave pulses) were delivered at a rate of 4/sec and at an intensity equal to the motor plus sensory thresholds.[8]

For median nerve SEPs, recording electrodes were positioned over Erb's point, the fifth cervical spinous process (SC-5), and over the left and right central scalp areas (C_3 or C_4, International 10-20 system). A reference electrode was placed at the mid-frontopolar area (Fp_z). A fourth recording channel measured the activity between either C_3 or C_4 and the contralateral shoulder.

For peroneal or posterior tibial SEPs, recording electrodes were placed over the spinous processes of the first and third lumbar vertebrae (L-1, L-3) and the ninth and twelfth thoracic vertebrae (T-9 and T-12), and on the scalp at the midline vertex (C_z), C_3, and C_4. A typical four-channel recording montage was L-1 - L-3, T-12 - T-9, C_3 or C_4 - C_z, and C_4 - C_3.

Responses were sampled over 50 msec using a bin width of 200 μsec. Low and high frequency filter settings (−3dB) were 30 Hz and 1,500 Hz respectively. Each response represented the average of 500–1,000 stimuli and was replicated at least once to ensure reproducibility.

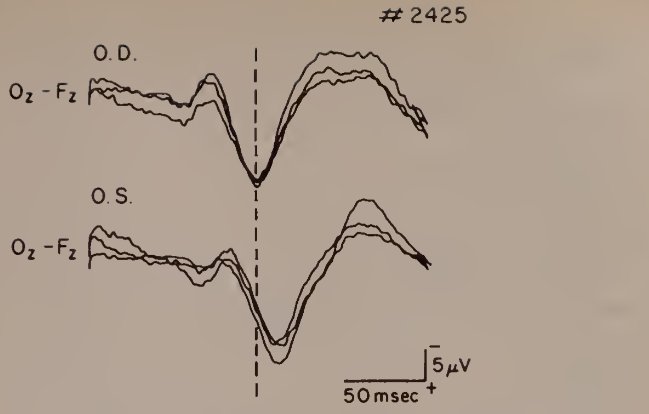
Visual evoked potentials. VEPs were recorded following monocular stimulation using an alternating checkerboard pattern with a reversal rate of 1/sec. Individual checks subtended 23.4′ and the full field subtended 12° at the patient's eye. Luminance of the white checks was 138 and of the black checks 0.94 candela per square meter. Responses were sampled over 200 msec from recording electrodes placed at the mid-occiput (O_z), MP_z (midposition between O_z and the standard midline parietal electrode placement, P_z) and Fp_z referenced to the mastoid (M_1 or M_2). A fourth channel recorded the response between O_z and Fp_z. Band pass was 1 to 70 Hz (−3dB). A bin width of 1 msec was used. Each response represented the average of 100 stimuli and was replicated at least once.

Brainstem auditory evoked potentials. BAEPs were obtained using monaural rarefaction or alternating clicks at a frequency of 11/sec and an intensity of 70 dBSL. The nonstimulated ear was masked with white noise delivered at an intensity 40 dB less than that used for click stimulation. Recordings were obtained between electrodes over the ipsilateral and contralateral mastoid bone referenced to C_z. The sampling time was 10 msec and the bin width 20 μsec. Filter settings were 150 Hz and 3,000 Hz (−3dB): Each response represented the average of 2,000 stimuli and was replicated at least once.

For all evoked potentials, analysis was based on measurements of the absolute and interpeak latencies of the major waveform components. A patient's response was considered abnormal if one or more major components were absent, or if latency measurements deviated from control values by more than three standard deviations.

RESULTS

Evoked potential studies in a representative patient with multiple sclerosis are shown in Figures 1 and 2. Evoked potential findings in the entire group are summarized for each diagnostic category in the Table. Several points deserve emphasis. First, the incidence of abnormal SEPs might have been even higher in the multiple sclerosis and cervical spondylosis groups if every patient had been completely evaluated by recording responses from both upper and lower extremities. The importance of this is illustrated by six patients who had normal median nerve SEPs but abnormal SEPs following peroneal or posterior tibial nerve stimulation. Second, 13 patients (76%) with probable multiple sclerosis had abnormal VEPs, electrophysiologic evidence for a second lesion outside the spinal cord. Third, while 26 patients had electrophysiologic evidence of impaired somatosensory function, only eight of these were felt on further clinical testing to have mild but unequivocal alteration in vibratory or position sense.

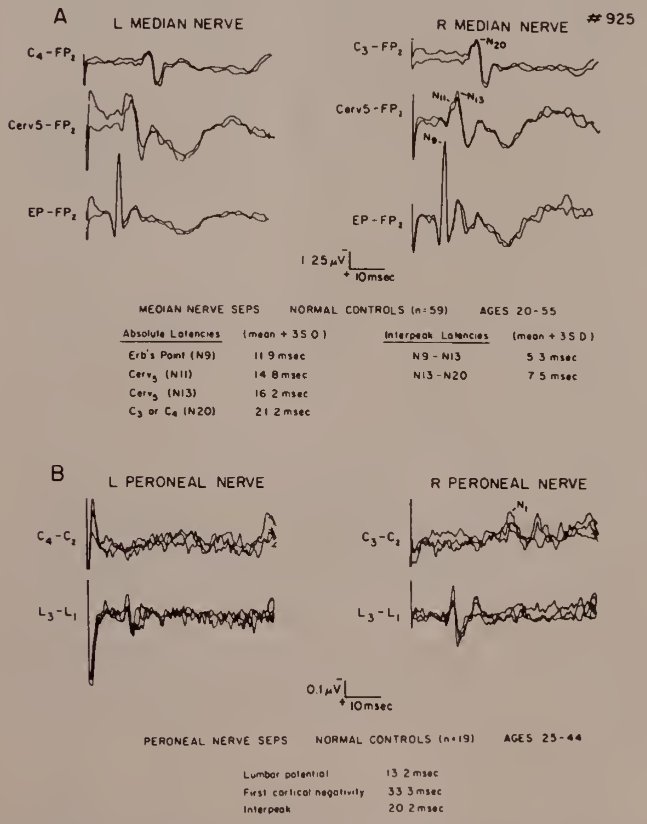


Normal P_{100} latency at O_z (+3 S.D.) <115 msec

Normal P_{100} interocular latency difference (+3 S.D.) <7 msec

(n=76, ages 15-60 years)

FIGURE 1. Pattern-reversal visual evoked potentials obtained in a 39-year-old woman with presumed multiple sclerosis. She had no history of visual symptoms. Although absolute latencies of right and left eye P_{100} waves are within 3 SD of control values, interpeak latency difference of 14 msec is abnormal indicating conduction velocity is slowed in left optic nerve.



MEDIAN NERVE SEPS NORMAL CONTROLS (n=59) AGES 20-55

Absolute Latencies	(mean + 3 S D)	Interpeak Latencies	(mean + 3 S D)
Erb's Point (N9)	11 9 msec	N9 - N13	5 3 msec
$Cerv_5$ (N11)	14 8 msec	N13 - N20	7 5 msec
$Cerv_5$ (N13)	16 2 msec		
C_3 or C_4 (N20)	21 2 msec		

PERONEAL NERVE SEPS NORMAL CONTROLS (n=19) AGES 25-44

Lumbar potential	13 2 msec
First cortical negativity	33 3 msec
Interpeak	20 2 msec

FIGURE 2. Somatosensory evoked potentials to median (A) and peroneal nerve (B) stimulation in the same patient. Responses to median nerve stimulation are normal as is response obtained following stimulation of right peroneal nerve. Following stimulation of left peroneal nerve, however, no cortical response was obtained. This patient had no sensory symptoms.

Summary of Evoked Potential Findings in 45 Patients With Progressive Spastic Paraparesis

Diagnosis	SEP$_M$	SEP$_P$	VEP	BAEP
Probable multiple sclerosis 17 patients	7/15	5/8	13/17	0/9
Cervical spondylosis 5 patients	3/5	1/1	0/2	0/2
Motor neuron disease 2 patients	0/2	0/1	0/2	0/1
Familial spastic paraplegia 2 patients	1/1	...	0/2	...
Spinal cord tumor or arteriovenous malformation 3 patients	0/2	2/3	0/2	0/1
Neurosyphilis 1 patient	0/1	...	...	...
Paraneoplastic syndrome 1 patient	0/1	1/0	...	...
Syringomyelia 1 patient	0/1	...	0/1	1/1
Undiagnosed 13 patients	4/13	3/3	1/12*	0/9

Fractions indicate the number of patients with abnormal tests/number of patients tested.

* Includes one patient with post-traumatic blindness.

Abbreviations: SEP$_M$ = median somatosensory evoked potential; SEP$_P$ = peroneal or posterior tibial somatosensory evoked potential; VEP = visual evoked potential; BAEP = brainstem auditory evoked potential.

DISCUSSION

This study, as other recent reports, found evoked potential testing useful in the evaluation of patients with slowly progressive spastic paraparesis and no signs of disease outside the spinal cord. EPs assist in segregating specific diagnostic categories from the otherwise large group of undiagnosed myelopathies of late onset.

We confirmed a good correlation between presence of oligoclonal bands in the CSF and evoked potential abnormalities. Trojaborg et al[9] and Miller et al[10] emphasize that the combination of evoked potential studies and CSF oligoclonal bands or elevated immunoglobulins allows the diagnosis of multiple sclerosis to be made with greater certainty than can often be achieved on clinical grounds alone. Poser et al[11] have likewise recognized this in their proposal of new diagnostic criteria for multiple sclerosis. Using this classification, multiple sclerosis can be definitely diagnosed in a patient with clinical or paraclinical (eg, evoked potential) evidence of one lesion and CSF oligoclonal bands not derived from the serum. In the case of an undiagnosed progressive spinal cord syndrome, for example, an abnormal VEP is especially useful, as it indicates a second, anatomically remote lesion.[12] Nonetheless, it is important to be cautious in making even a possible diagnosis of multiple sclerosis in someone with spastic paraparesis on the basis of evoked potential abnormalities without appropriate cerebrospinal fluid changes since abnormal VEPs have been reported in patients with familial spastic paraplegia.[13-15] A careful and reliable family history is essential, and in certain cases examination and testing of close relatives may be indicated.

The overall proportion of patients with abnormal VEPs was 31% in our series, a figure similar to the 35% reported by Blumhardt et al[12] in patients with spastic paraparesis of at least six months duration. In combination with other data, however, specific likely diagnoses were possible in 71% of our cases.

Abnormalities of the somatosensory evoked potential have been described in lesions affecting the somatosensory system from the peripheral nerves to the sensory cortex.[16] Experimental and clinical evidence indicates that the SEP, as conventionally recorded, represents afferent sensory volleys mediated principally by the dorsal column-lemniscal system,[17-20] although a recent study suggests that extralemniscal pathways may contribute to the scalp-recorded SEP to a greater extent than previously thought.[21] No patient in our group with abnormal vibratory or position sense had normal SEPs. Of greater interest, however, were 17 patients with normal sensory examinations who had abnormal SEPs indicating subclinical dysfunction of the somatosensory pathways. It is also clear from our study and the work of others that SEPs obtained following stimulation of peropheral nerves in both upper and lower limbs substantially increases the yield of abnormal responses in patients with progressive spastic paraparesis.

BAEPs were abnormal in only one patient with syringomyelia and in none with presumed multiple sclerosis. Khoshbin and Hallett[3] also reported that BAEPs were less useful than either VEPs or SEPs in patients with multiple sclerosis.

Four of five patients with cervical spondylosis had abnormal SEPs confirming earlier reports that SEPs can yield valuable diagnostic information in patients with mechanical compression and distortion of the cervical cord.[3-7] Comparison of SEP abnormalities in patients with cervical spondylosis with those from patients with multiple sclerosis revealed no consistent differences. Neither amplitude, as suggested by Siivola et al[7] nor preferential involvement of the N_{11} component, as reported by el-Negamy and Sedgwick[4] reliably discriminated between the two conditions in our population.

Abnormal EPs should exclude the diagnosis of motor neuron disease, and as expected, our two patients with motor neuron disease had normal EP studies. One note of caution is indicated, however. Since both motor neuron disease and cervical spondylosis are relatively common neurologic disorders, it should not be surprising if abnormal visual evoked potentials are occasionally recorded as independent but unrelated phenomenon. Our sample group would seem to indicate that progressive spastic paraparesis is an infrequent presentation of motor neuron disease in the absence of clinical evidence of lower motor neuron involvement. This is also the conclusion of Ungar-Sargon et al[22] in a major review.

In 13 patients, no diagnosis was made at the time of discharge. None of these had a complete battery of evoked potential tests, and four did not have CSF analyzed for oligoclonal bands. Some of these patients may well prove to have multiple sclerosis or primary lateral sclerosis, although Beal and Richardson[23] have stressed the rarity of the latter condition.

We conclude the EP abnormalities occur in a substantial number of patients with progressive spastic paraparesis. EPs are useful in diagnosis of these patients (1) to confirm the integrity, or conversely document the involvement, of the dorsal column-lemniscal system when the sensory examination is normal or equivocal; and (2) to provide electrophysiologic evidence for additional lesions outside the spinal cord. For example, in patients with probable multiple sclerosis, visual evoked potentials were abnormal in 76%.

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Diagnosis of deep vein thrombosis by phleborheography in a community hospital

MICHAEL A. RICCI, MD, BRADFORD C. FULLER, LPN, JOSEPH L. BYRNE, MD, DONALD HASWELL, MD

ABSTRACT **Phleborheography (PRG) is a simple plethysmographic technique utilized in the diagnosis of acute deep vein thrombosis. Over a period of 29 months, 413 examinations were done; 64 limbs were also evaluated by venography. Accuracy of the phleborheographic exam was determined to be 83% (53/64) with a sensitivity of 77% (10/13) and a specificity of 84% (43/51). Three false negatives occurred while eight tests were falsely positive. The predictive value of a positive test was 56%; however, the negative predictive value was 93%. It is apparent that a negative PRG is useful in ruling out acute lower extremity thromboembolic disease. A practical approach to the problem of diagnosis utilizing PRG is presented.**

(NY State J Med 1984; 84:72-73)

INTRODUCTION

Phleborheography was introduced in 1973 as a noninvasive method for the diagnosis of deep vein thrombosis.[1] It is a flow-dependent technique utilizing air-inflated cuffs about the abdomen, thigh, upper calf, mid-calf, lower calf, and foot. Sequential inflation and recording beneath the cuffs produce a tracing attributable to changes in venous volume. The test is a good alternative to contrast venography which is invasive, painful, and occasionally associated with allergic reactions and thrombosis. To determine the clinical usefulness of PRG in the community setting, a review of all phleborheographic examinations done at St. Joseph's Hospital Health Center was undertaken.

PATIENTS AND METHODS

The records of 413 patients referred to the vascular laboratory for phleborheography (PRG) between October 1980 and February 1983 were examined. Only those patients with suspected deep vein thrombosis who underwent venography within 48 hours of PRG were selected for study.

The Grass-Cranley phleborheograph (Model PRG) manufactured by the Grass Instrument Company (Quincy, MA) was used. The instrument and method of examination have been described previously.[1,2] Major criteria for the diagnosis of acute thrombosis included absent, nonphasic, or diminished respiratory waves and baseline elevation. Minor criteria included prominent arterial pulsations and poor or absent foot emptying. Interpretation was done primarily by four surgeons without the knowledge of venographic results. Review for the purpose of this study was done independently by one of us (J.L.B.).

The technique of venography has also been previously described.[3] Criteria for diagnosis have been summarized as well.[3,4] Briefly, only a constant filling defect was considered diagnostic of acute deep venous thrombosis. Nonfilling of a vein or the entire deep venous system and abnormal collateral flow were not considered diagnostic but often indicated obstruction to flow. Since these patients were referred with the clinical suspicion of acute thrombosis, these findings were considered suggestive of thrombosis,[4] and, for the purposes of this study, a positive venogram. Radiographic interpretation was originally done primarily by one radiologist although a number were interpreted by any of five other staff radiologists. Review for this study was done by one of us (D.H.) without knowledge of the PRG result.

Analysis of data was done as suggested by Ransohoff and Feinstein.[5] Accuracy, sensitivity, and specificity as well as positive and negative predictive values were determined.

RESULTS

Forty patients had PRG and venography within 48 hours; 24 venograms were bilateral. Thus, a total of 64 extremities were available for study. The results are summarized in Table I.

The PRG and venogram agreed in 53 of 64 limbs, representing an accuracy of 83%. PRG was abnormal in 10 of 13 limbs with thrombosis (sensitivity, 77%) and normal in 43 of 51 limbs free of clot (specificity, 84%).

There were three falsely negative phleborheograms. One patient had a venogram revealing a nonfilling deep venous system with incompetent perforating veins. Two PRGs were interpreted as equivocal (3%). One of these had total occlusion of the deep venous system while the other revealed a small clot in the deep veins of the calf. Both equivocal PRGs were considered falsely negative.

Eight extremities had an abnormal PRG in the face of a normal venogram. One patient was in pain due to a herniated disk and was unable to cooperate with the examination; both limbs had an abnormal PRG. Another patient suffered a hip fracture one week before the study and had extensive soft tissue swelling in the thigh. In another patient receiving anticoagulant therapy a hematoma of the calf was subsequently aspirated. A young athlete with a calf muscle injury and soft tissue swelling had a falsely positive examination. The explanation

TABLE I. Results of Phleborheography (PRG) and Venography in 64 Limbs

	Venography		
	Positive	Negative	Total
PRG			
Positive	10	8	18
Negative	3	43	46
	13	51	64

Accuracy 83%; Sensitivity 77%; Specificity 84%; Positive predictive value 56%; Negative predictive value 93%.

TABLE II. Location of Thrombi

	PRG		
	Positive	Negative	Total
Calf only	2	1	3
Proximal only*	3	0	3
Calf and proximal	5	3	8

* The proximal venous segment includes the popliteal vein, iliofemoral segment, and vena cava.

From the Departments of Surgery (Drs Ricci, Byrne) and Radiology (Dr Haswell, Mr Fuller), St. Joseph's Hospital Health Center, Syracuse, New York.

Address correspondence to Dr Ricci, Resident, Department of Surgery, Robert Packer Hospital, Guthrie Square, Sayre, PA 18840.

for the remaining three false positive results could not be determined.

The predictive value of a positive PRG result was 56% (10/18) while the negative predictive value was 93% (43/46).

Of the 13 thrombi detected by venography, PRG successfully identified two of three thrombi confined to the calf. All three thrombi confined to the proximal venous system were detected by PRG, while five of seven limbs with proximal and distal thrombosis were detected. (Table II).

DISCUSSION

Phleborheography has proved to be a useful adjunct in evaluating patients with suspected deep venous thrombosis. Comerota et al[2] have recently reviewed their experience with PRG in 21,626 extremities. In 709 limbs undergoing venography, sensitivity was 92% (247/268) and specificity, 95% (418/441). Less than 1% of the total were equivocal. Of 23 false positive results, 11 were attributed to errors in technique or interpretation. False negative results occurred in 21 cases, most commonly due to isolated calf vein thrombosis.

The diagnostic accuracy of 83% in this study is less than that reported by Comerota et al.[2] This may simply be a reflection of their extensive experience with the technique. The venographic criteria adapted for this study may also have contributed to our less accurate results. It was our aim to define the usefulness of PRG to the clinician who must decide to initiate therapy. Faced with an acutely symptomatic leg and a venogram consistent with, but not diagnostic of, venous thrombosis, most practitioners would initiate anticoagulant therapy pending further study. In reality, this situation may represent chronic venous disease with well developed collateral flow; this could explain the two false negative results with nonfilling and occluded deep venous systems.

The greatest value of the PRG may lie in a negative result. A negative predictive value of 93% provides reasonable assurance that a limb is free of thrombosis. A positive test did not provide the same degree of accuracy (56%). An incomplete examination or local factors, such as hematoma or soft tissue swelling, can lead to a false positive PRG. If these variables can be excluded, it is likely a positive test will be more useful.

Reliability of PRG below the level of the popliteal vein has been questioned. Bynum et al[6] found a false negative rate of 31% in their evaluation of 143 limbs. Of 11 cases of thrombosis missed by PRG, four involved the popliteal or distal femoral veins while the remaining seven were in the calf only; six of these were in the muscular venous plexuses, sparing the main venous channels. However, it remains controversial whether isolated calf vein thrombi need to receive anticoagulant therapy. It has been suggested that most such thrombi are self-limiting, undergoing spontaneous lysis or giving rise to insignificant, subclinical emboli.[7]

It has been our approach to utilize PRG as a first line diagnostic test when deep vein thrombosis is suspected. A negative result virtually rules out the diagnosis and obviates the need for anticoagulation. Venography would be obtained only if very unusual circumstances existed. An abnormal PRG is considered sufficient evidence for initiation of anticoagulant therapy; if the conditions known to produce false positive examinations can be excluded and clinical suspicion remains high, a venogram is not obtained. If this is not possible, venography is recommended before committing the patiet to long-term anticoagulation therapy. Equivocal results necessitate venography. This approach appears to avoid, safely, the expense and morbidity of venography in patients with normal deep venous systems. Furthermore, it provides adequate justification for beginning a potentially hazardous therapy.

Acknowledgments. We would like to thank Syed Zaman, MD and James Meade, MD for their critical comments, and Anne Fogarty for secretarial assistance.

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An abnormal blood count in a 26-year-old man with Hodgkin's disease in remission

CASE PRESENTATION

Joanne Holland, MD (Resident, Medical Service): A 26-year-old-man with stage IV B Hodgkin's lymphoma in remission was admitted for evaluation of an abnormal blood count.

The patient had been in good health until four years earlier when he developed gradual onset of weakness, lassitude, persistent night sweats, weight loss, and left-sided chest pain. His prior medical history included only a herniorrhaphy and a tonsillectomy in early childhood. Medical evaluation shortly after the onset of symptoms revealed the presence of a mediastinal mass; biopsy of a supraclavicular lymph node was diagnostic of nodular sclerosing Hodgkin's disease. As a result of laparotomy and splenectomy, splenic involvement with Hodgkin's disease was identified pathologically, and his disease process was classified as stage III B. Two cycles of C-MOPP therapy (cyclophosphamide, vincristine, procarbazine, prednisone) were administered without response; following transfer to the Northport Veterans Administration Medical Center, he received 12 cycles of MOPP therapy (nitrogen mustard, vincristine, procarbazine, prednisone) with complete response.

A year after the onset of his symptoms, he was readmitted for evaluation of a persistently abnormal chest x-ray. After an unsuccessful diagnostic effort with the aid of bronchoscopy, a left thoracotomy revealed mediastinal involvement with Hodgkin's disease of the nodular sclerosis type. He was treated with 4,000 rads to the mediastinum with complete radiographic resolution of the lesion.

Three months later, however, he began to complain of back pain; a bone scan showed increased uptake in the T-3 vertebral body, with collapse of the vertebral body of T-4. Following local radiation therapy, his bone pain abated; his Hodgkin's disease was reclassified as stage IV B. Chemotherapy (adriamycin, bleomycin, vinblastine, DTIC) was continued in the Oncology Clinic for the following ten months, with complete remission. Gated-pool scan indicated normal cardiac ventricular function, with an ejection fraction of 55%.

Approximately four years after the onset of his disease, he was found on routine laboratory examination to have a white blood count of 28,000/mm^3, with 24% polymorphonculear leukocytes, 7% band forms, 21% lymphocytes, 18% blast forms, 3% eosinophils, and 27% monocytes with nucleated red blood cells. He denied complaints of weakness, weight loss, fever, or headache.

Physical examination at that time showed the patient to be thin, but in no distress. His temperature was 37.5°C (99.6°F), pulse 60 per minute and regular, respiratory rate 12 per minute, and blood pressure 100/60 mm Hg. No skin rash was present; enlarged firm 2 × 2-cm lymph nodes were observed in the posterior cervical chain, unchanged from previous examinations; but similar palpable nodes were now present in the right axilla and in the inguinal regions. The remainder of the physical examination was entirely within normal limits, except for the scars of previous surgical procedures.

A repeat blood count confirmed the new hematologic findings; the hemoglobin and red blood cell counts were normal. The prothrombin time and partial thromboplastin time were within normal limits. Urinalysis was normal; blood chemical tests showed only a lactic dehydrogenase of 458 IU (normal, 60 to 200 IU). On review, the chest x-ray films taken over the preceding eight months showed no progressive changes; there were surgical clips in the left mediastinum. The heart size was normal and the lungs were clear. A gallium scan showed no abnormal concentrations of radionuclide.

Richard Balter, MD (Medical Service): Our present-day advances in the diagnosis and staging of Hodgkin's disease, as well as advances in radiation therapy and in the protocols of chemotherapeutic agents, have offered patients an increase in survival and higher cure rates. A small but increasing number of patients who have benefitted from this increase in longevity are beginning to display second malignancies, usually years after the initial diagnosis of Hodgkin's disease was made, at a time when the original disease is in remission or is quiescent. It could be argued that in these patients we are actually witnessing the natural history of the Hodgkin's disease process itself. It has become increasingly clear, however, that the complication of a second neoplasm might very well be due to the current therapy for Hodgkin's disease, particularly ionizing radiation and alkylating agents.

The case we are confronted with involves a young man whose diagnosis of Hodgkin's disease was made at age 22. He was treated with multiple chemotherapeutic regimens and radiation therapy, and four years later presented with an abnormal white blood cell count and peripheral smear. At that time he was asymptomatic and was felt to be in re-

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Based on the clinicopathologic conference (CPC) held at Northport Veterans Administration Medical Center, Northport, New York, July 25, 1983.

Moderator: Edmund Gogel, MD.

Clinical Discussion: Richard Balter, MD, instructor in medicine, State University of New York at Stony Brook.

Pathology Presentation: Carl F. Ilardi, MD, assistant professor of pathology, State University of New York at Stony Brook.

Editor: JOHN T. FLYNN, MD.

Address correspondence to Dr Flynn, Consulting Editor, *New York State Journal of Medicine*, PO Box 5404, 429 Lakeville Rd, Lake Success, NY 11042.

mission.

We will ask Dr Bagnasco to review the x-rays.

Francis M. Bagnasco, MD (Associate Professor of Radiology, SUNY at Stony Brook): The anterior-posterior chest x-ray taken four years ago shows a large mass overlying the left hilar area which on the lateral view is clearly in the anterior mediastinum. A CT scan of the chest taken at that time shows the very large superior mediastinal mass occupying the entire left upper lung field anteriorly; the scan shows no evidence of retroperitoneal, mediastinal, or hilar node enlargement.

After his treatment with chemotherapy, he returned with a mass which in superficial appearance is similar to the first mass but is actually now a hilar mass. The lateral view taken at that time shows the anterior mediastinum to be entirely clear. This hilar mass was then resected and subsequent chest films showed only the metallic clips at the operative site.

Dr Balter: At the age of 22, this patient presented with weakness, lassitude, night sweats, and weight loss. A supraclavicular node biopsy indicated the presence of the nodular sclerosing form of Hodgkin's disease. At staging laparotomy and splenectomy, he was found to have splenic involvement. Twelve courses of MOPP were administered, rather than the usual six courses, because of the persistently abnormal chest x-ray.

The patient was given 4,000 rads to the mediastinum, with complete resolution of the lesion on chest x-ray. Three months later, however, he was reclassified as stage IV B because of bony involvement and collapse of the fourth thoracic vertebra. Usually in Hodgkin's disease the spread is by continuity along lymphatic channels; splenic involvement can be secondary to spread from para-aortic nodes but together with bone involvement can alternatively result from hematogenous spread. The back pain responded to radiation and thereafter he received chemotherapy, including adriamycin, bleomycin, vinblastine, and DTIC. He appeared to be in complete remission until one year ago, when he developed an abnormal white blood cell count and peripheral smear, as noted on the protocol. At this time he was asymptomatic although his physical examination revealed posterior cervical, right axillary, and inguinal adenopathy. His chest x-ray did not show any evidence of recurrence in the central lymph nodes and we are told that he had no Auer rods on peripheral smear.

Most relapses of Hodgkin's disease occur during the first three years of therapy. In general, the conditions which increase the probability of relapse are increasing stage, systemic symptoms, and the presence of nodular sclerosis.[1] The patient with Hodgkin's disease with relapse is likely to show evidence of relapse in the site previously involved with the disease. If a new site is involved, it is likely to be adjacent to a previously involved site. In the case of the patient with central lymphadenopathy, relapse would commonly occur in the central lymph node sites. It is unusual for a patient with Hodgkin's disease to relapse in a visceral location that was not previously involved with the disease.

The first question which I will attempt to answer is: Can we relate or attribute this patient's abnormal white blood cell count to his Hodgkin's disease? The abnormal white count and the 18% blast forms on the peripheral smear are indicative of a pathological process within the bone marrow, suggestive of either a leukemic transition or a leukemic conversion. Hodgkin's disease can result in direct leukemic transition, with the occurrence of the so-called Reed-Sternberg-cell leukemia, a manifestation of uncontrolled Hodgkin's disease.[2] Such an event may be present early in the clinical course, even at the initial presentation. Patients with Hodgkin's disease who have Reed-Sternberg cells in the blood have a relatively grave prognosis and usually a rapid downhill course. In light of the fact that the patient developed the abnormalities of the blood count four years after the initiation of therapy at a time when the disease was quiescent, the notion of a Reed-Sternberg cell leukemia would be unlikely.

Other forms of hematologic neoplasm have been reported in Hodgkin's disease, specifically in patients who have received aggressive therapy with radiation as well as chemotherapy. These malignancies are complications of the synergistic carcinogenic effect of these treatment modalities, which can lead to a leukemic conversion within the bone marrow. The entity of acute nonlymphoblastic leukemia is the most common of the leukemias associated with Hodgkin's disease; in this situation, it occurs 25 times more frequently than do other forms of leukemia.[3] These leukemias tend to occur in patients who have been aggressively treated with chemotherapy and radiation, usually at a median of about 3.4 years after the initiation of therapy, at a time when the Hodgkin's disease is quiescent, perhaps even cured.

One important hallmark of this leukemic complication is the association with cytopenia, usually preceding the actual diagnosis of leukemia. In a study of a large number of patients who had acute nonlymphocytic leukemia associated with Hodgkin's disease, the median white blood count at the time of initial hematologic diagnosis was 3,400 cells per cubic millimeter, the hemoglobin was 7 g/dL, and the hematocrit 27%. The platelet count was 52,000.[3] In our patient, although the time-course and the aggressive therapy make this entity a likely possibility, I think that a normal hemoglobin, a normal hematocrit, and normal platelet counts would speak against this conversion.

Other forms of acute leukemia which have been reported in Hodgkin's disease are clearly less common than acute nonlymphocytic leukemia. I think that the possibility of acute lymphoblastic leukemia should be considered; however, it would be unlikely in the presence of an otherwise normal hematologic picture. For the sake of completeness, I would like to mention chronic lymphocytic leukemia, which usually will precede the diagnosis of Hodgkin's disease when it is associated therewith. The blasts that were seen on the peripheral smear in this case would not suggest this diagnosis. Finally, there have been cases of aggressively treated patients with Hodgkin's disease who have developed chronic myelocytic leukemia. There is nothing in this case protocol that would allow me to rule out this possibility; but in the light of its rarity, and in the absence of important clinical data in the protocol, such a diagnosis would be quite unlikely.

There have been isolated reports of Hodgkin's disease and non-Hodgkin's lymphoma occurring simultaneously, in the same lymph node site or in the same organ, or in separate sites.[4] More recently, there have been reports of non-Hodgkin's lymphoma following the aggressive treatment of patients with Hodgkin's lymphoma. In a study at Stanford University Medical Center, six patients who were aggressively treated for Hodgkin's disease developed non-Hodgkin's lymphoma in a period of from 44 months to 124 months after the initiation of the aggressive therapy. Two of the six patients had developed diffuse histiocytic lymphoma, while four had undifferentiated lymphomas. Five of the six patients had involvement of the abdomen or of the gastrointestinal tract; and one patient had peripheral lymphadenopathy.[4] Certainly this is not the course that our patient has taken. Infiltration of the bone marrow and peripheral blood is rare in Hodgkin's disease but is a relatively common phenomenon in non-Hodgkin's lymphoma.

In patients with non-Hodgkin's lymphoma who develop tumor conversion, the type of abnormal cell which they will develop depends on the histologic classification of their disease. For example, patients with well-differentiated lymphocytic lymphoma will develop cells which very much suggest chronic lymphocytic leukemia; patients with poorly differentiated lymphocytic lymphoma will develop cells which appear very much like those of acute lymphoblastic leukemia. However, there is a definite subgroup of patients with non-Hodgkin's lymphoma who develop abnormal cells which are morphologically unlike those of any other form of leukemia. These cells are large lymphocytic cells with large nuclei and abundant cytoplasm—so-called lymphosarcoma cells. This type of cell has been reported in cases of Hodgkin's disease which have been treated aggressively with both radiation and chemotherapy.[5] In fact, on a peripheral smear, it would be very difficult to differentiate these lymphosarcoma cells from blasts of any other type of leukemia. It is my impression that it was this type of lymphosarcoma cell which was present on the peripheral smear of this patient. I believe that this patient was treated aggressively for Hodgkin's disease four years earlier and then developed lymphosarcoma-cell leukemia; the absence of pancytopenia would be consistent with this diagnosis. The definitive diagnostic procedure here would be, then, a bone marrow biopsy and I believe that it would reveal lymphosarcoma cells.

In conclusion and as a small aside, the differential that I have discussed here today is basically that of the complications of therapy for Hodgkin's disease, which in no way should overshadow the remarkable gains which medicine has made in prolonging lives of patients with Hodgkin's disease.

Clinical Diagnoses

Hodgkin's disease, originally stage III B, with post-treatment relapse to stage IV B, treated aggressively with radiation and chemotherapy.

Lymphosarcoma-cell leukemia, secondary to aggressive radiation therapy and chemotherapy.

Pathology Presentation

Carl F. Ilardi, MD (Laboratory Services): The sections of lymph nodes removed at the thoracotomy in 1979 show cellular nodules, delineated by wide birefringent fibrous bands which are one of the hallmarks of nodular sclerosing Hodgkin's disease. Within the cellular areas there were occasional Reed-Sternberg cells of the classical variety and also others which are the lacunar-cell variant seen in nodular sclerosing Hodgkin disease (Fig 1). Lymphocytes, neutrophils, plasma cells, and eosinophils compose the remainder of the cellular population.

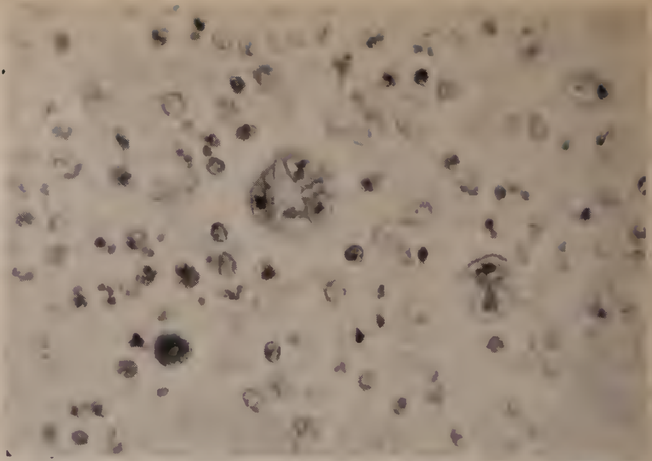
FIGURE 1. High magnification of a classic Reed-Sternberg cell (right) and a multilobated lacunar cell variant (left).

At the time of the thoracotomy, a bone marrow biopsy revealed the marrow to be only slightly hypocellular for a male of this age, perhaps related to his previous chemotherapy (Fig 2). There was no evidence of leukemic involvement of the marrow and no evidence of Hodgkin's disease. By contrast, the peripheral blood smear, taken one year ago—that is, three years after the onset of Hodgkin's disease—shows 15% blast forms with a total white blood count of 28,000. The diagnosis of acute myelomonocytic leukemia was based on three general findings: the morphology of the cells, the results of cytochemical staining, and the elevated serum muramidase. An elevation of the serum muramidase is indicative of cellular differentiation along monocytic lines. In this patient, the serum muramidase was approximately 12 μg/mL whereas the normal range is 3 to 7 μg/mL.

The accompanying peripheral blood smear showed very large blast cells with nucleoli, indentations and folding of the nuclei, and a grayish cytoplasm (Fig 3). These features suggest the monocytic origin of these cells. Other cells had very fine cytoplasmic granules within them. A bone marrow

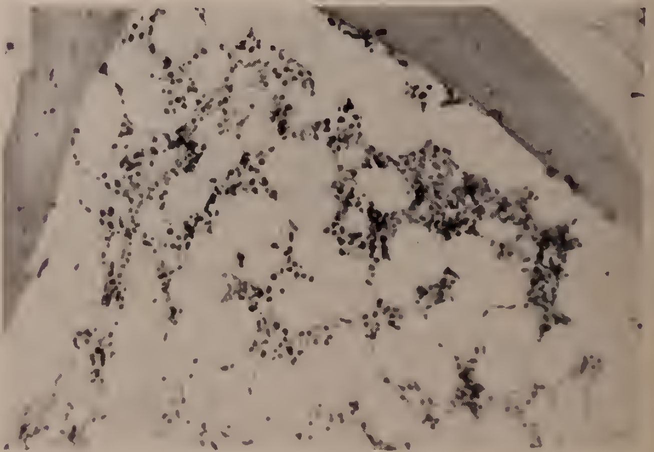
FIGURE 2. Hypocellular bone marrow.

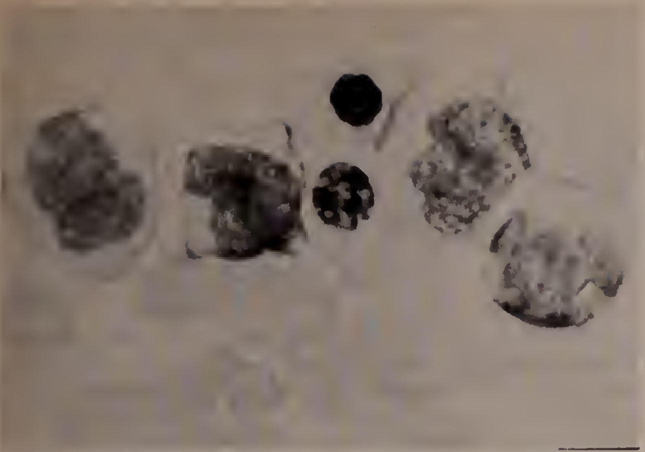

FIGURE 3. Peripheral blood smear one year prior to death. Note angulated cytoplasm and deeply folded nuclei in blasts.

aspirate at this time showed replacement of marrow by large numbers of these blast cells, some of them granulated, and others having a monocytoid appearance.

Histochemical studies of the blast forms in the peripheral blood and bone marrow are consistent with myelomonocytic origin of these cells. The Sudan black B stain, which stains the phospholipids in the azurophilic and specific granules of myelocytic cells, resulted only in a very fine stippling of the blast forms in this patient. By contrast, this stain will blacken the granules of polymorphonuclear leukocytes quite strikingly, and myelocytic cells in general will stain much more heavily than we find in this patient. Myelomonocytic cells, however, present the kind of very light staining characteristics which the blast cells demonstrate in this case.

The naphthol AS-D acetate stain demonstrates nonspecific granules which can be found in both monocytes and myelocytes; however, if the tissue is pretreated with fluoride, the staining of monocytic cells is inhibited, whereas that of myelocytic cells is not. If the cell is myelomonocytic, pretreatment with fluoride will result in some inhibition of staining; in this case this combination of techniques demonstrated a mild amount of staining in the blast cells, so we believe them to be myelomonocytic.

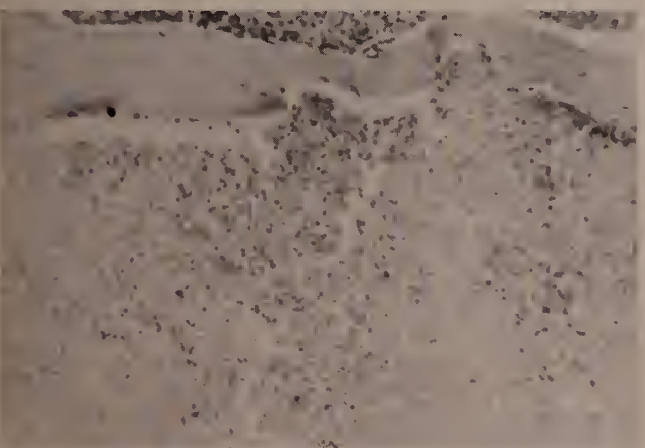

FIGURE 4. Total replacement of bone marrow by blasts, five months before death.

Five months ago, the patient presented with a white blood cell count of 80,000, the highest throughout his entire clinical course, with the presence of many more blasts in the peripheral blood, compared with smears taken nine months earlier. The bone marrow which accompanied this peripheral blood picture was almost completely replaced by a population of myelomonocytic blast forms (Fig 4).

Mohammad H. Zarrabi, MD (Special Hematology/Oncology Division, Medical Service): This patient had been very closely followed by all members of the Hematology Department. Initially the patient refused chemotherapy for his leukemia, but when he was presented with the option of bone marrow transplantation, he agreed to receive chemotherapy. He achieved complete remission after chemotherapy with high doses of ARA-C. He was then transferred to the Fred Hutchinson Cancer Research Center in Seattle, Washington, where he underwent a successful bone marrow transplant from his HLA-matched brother. His post-transplant course was complicated by graft-versus-host disease. I am sorry to say that he expired from a cytomegalovirus infection, two months after a bone marrow transplant was performed.

I have been asked to discuss secondary leukemia following treatment with chemotherapy and radiotherapy, a complication in which we have been interested since early 1972. Acute myeloid leukemia or one its variants is being reported with increasing frequency as a second neoplasm in patients treated for Hodgkin's disease,[6] multiple myeloma, non-Hodgkin's lymphoma, chronic lymphocytic leukemia, breast cancer, ovarian cancer, other neoplasms, and even in patients with non-neoplastic diseases treated with cytotoxic chemotherapy.

Second leukemia has many of the characteristics mentioned by Dr Balter. It often is preceded by a period of pancytopenia or dyserythropoiesis or both with or without the presence of ringed sideroblasts in the bone marrow. These changes may be related to previous chemotherapy. The syndrome also is associated with refractoriness to antileukemic chemotherapy and with a very short survival. There is a disproportionately high frequency of the myelomonocytic or moncytic variety of acute leukemia with an accompanying increase in serum or urinary muramidase levels or both. Chromosomal aberrations may occur, mostly hypodiploidy of chromosomes 3, 7, and 9, but also hyperdiploidy.

Acute myeloid leukemia or one of its variants as a late complication of Hodgkin's disease has been reported in several large series with a frequency of 1% to 2%.[7] Patients who receive radiation therapy in addition to chemotherapy are at increased risk. If a patient first receives intensive chemotherapy and later needs radiation therapy, the incidence of second leukemia is about what one would expect; however if a patient is first given radiotherapy, then develops a relapse of Hodgkin's disease and therefore is subsequently given chemotherapy, the incidence of leukemia is much higher.[8] The types of drugs used are also important. Alkylating agents, procarbazine and the nitrosoureas are the most common offenders, although antimetabolites and newer agents such as daunorubicin, adriamycin, and bleomycin may also be leukemogenic. Finally the relative risk increases with time; the mean interval from the initial diagnosis of Hodgkin's disease to the development of acute leukemia is 73.4 months.[1]

Edward Gogel MD (Medical Service): Do different cell-types of Hodgkin's disease have different complication rates of second leukemia? Does nodular sclerosis, for example, predispose to second leukemia more readily than lymphocyte-depletion or other cell-types of Hodgkin's disease?

Dr Zarrabi: No.

Dr Gogel: Dr Balter had ruled out myelomonocytic leukemia largely on the basis that the patient presented with an elevated white blod cell count rather than pancytopenia. How frequent is the type of hematologic presentation which this patient offered?

Dr Zarrabi: These patients do often have pancytopenia prior to the occurrence of leukemia, but more cases presenting with a normal blood count are being seen. When you look at the laboratory data given in this protocol, you should bear in mind that the patient had 27% monocytes, or monocytoid cells. In lymphosarcoma-cell leukemia you do not find this type of differential white cell count, although that possibility should definitely be considered.

Dr Gogel: This patient, following the diagnosis of leukemia, refused treatment for about eight months, and the decision then was to attempt bone marrow transplantation. Do you feel that this is the treatment of choice with second leukemia? If so, why?

Dr Zarrabi: The prognosis of this type of leukemia is very very poor. The median survival of such patients is about three months, irrespective of what treatment you try. Chemotherapy with high-dose cytosine arabinoside led to a remission of the leukemia in this patient, but we felt that he would die very soon. We communicated with the Fred Hutchinson Cancer Research Center in Seattle, Washington, where they are trying to treat these patients with bone marrow transplantation, but there is no actual definitive data about such efforts at treatment. We did not have much hope to begin with, but it was the only chance we had.

Dr Balter: Myelomonocytic leukemia would be among the most common types of leukemia in such cases as this, but it was the absence of the pancytopenia that deflected me from the correct diagnosis.

Dr Gogel: In looking back on his entire clinical course, is there anything that could have been done differently, either in the initial type of chemotherapy or in the combination of radiation and chemotherapy which you indicate tends to increase the risk of second leukemia?

Dr Zarrabi: In the recent review which I have offered here as a reference,[7] I have emphasized that we should not let the patient die from the original malignant disease. If we do not treat the original Hodgkin's disease, the patient will die from that condition. So you have to take a chance. This patient had a poor prognosis because he did not remit with conventional treatment, but required 12 cycles instead of the usual six. He had to be given radiation twice. These facts would place him in the group with a poor prognosis due to the increased likelihood of a subsequent acute leukemia. Still, under the circumstances we had no other choice but to give him these treatments.

FINAL DIAGNOSES

Hodgkin's disease, nodular sclerosis type, stage III B, with post-therapy relapse to stage IV B, subsequently treated aggressively with radiation and chemotherapy.

Acute myelomonocytic leukemia, secondary to aggressive radiation and chemotherapy, treated with cytosine arabinoside, with remission.

Thrombocytopenia, secondary to the preceding diagnosis.

Bone marrow transplant, followed by graft-versus-host reaction, and by terminal respiratory distress syndrome secondary to cytomegalovirus infection.

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Henri Dagonet

Pioneer of psychiatric photography

AARON H. ESMAN, MD

The name of Henri Dagonet does not appear in the standard English language histories of psychiatry. This fact is not surprising, given the dominant influence on American psychiatry of the great central European systematizers—Kraepelin, Bleuer, Krafft-Ebbing and, later, of Freud, Jung, Adler, Binswanger, and other German-language innovators.

Still, Dagonet deserves to be remembered. A follower in the humane tradition of Pinel and Esquirol, he was the author of an influential textbook of psychiatry that went through three editions.[1] According to Gilman,[2] the second edition, published in 1876, was the first such textbook that "made extensive use of the newer photogravure process to reproduce photographs directly"; as such, it was a significant contributor to the development of the then popular concept of physiognomic diagnosis. Some of these photographs will appear further on.

BIOGRAPHY

The biographic data cited here are drawn from Semelaigne[3] (author's translation).

Henri Dagonet was born February 4, 1823, at Chalons-Sur-Marne, where his father directed the asylum he had founded. After pursuing medical studies in Paris Dagonet enrolled as an intern at the asylum of Fains; from there he moved to the asylum at Maréville. His inaugural thesis, submitted May 11, 1849, was entitled "Medico-Legal Considerations on Mental Alienation." The next year, at age 28, he obtained the position of doctor in chief of the Asylum of Stephansfeld and, in 1853, was named assistant professor of the faculty of medicine of Strasbourg. There he instituted the first course in mental illness, assiduously followed not only by medical students but also by the students of the military health school. These lessons were the origin of the *Elementary and Practical Treatise on Mental Illness* published in 1862.

Since the same influence could determine a variety of dissimilar forms of insanity, he rejected Morel's etiologic classification and, since most of the supposed lesions still remained unknown, he did not accept that of Parchappe which was based on pathologic anatomy. A perfect classification appeared to him to be impossible, and he adopted as a base clinical observation and symptomatology. "Today," remarked Christian[4] 40 years later, "we are still looking for an ideal classification, and our grandchildren, without doubt, won't see it any more than we do." These words remain true, and, if the proposed classifications are numerous, at least they give satisfaction to their authors. Dagonet's book was a great and legitimate success; the last edition was published in 1894.

In a letter addressed to the Medical Psychological Society in 1857, Dagonet indicated the difficulties encountered in the practice of legal medicine, complained of the lack of agreement in the use of terms and regretted the absence of a code of conduct. A question posed by a lawyer from Strasbourg had been particularly troubling to him. This person had asked him whether or not confessions made in a moment of madness by an accused person arrested for a serious crime could be of any value in the eyes of justice. Dagonet refused to consider madness as a frequent manifestation of remorse, and responded that justice in a particular case could not take account of the confession made by an accused person under the domination of a crisis of mental alienation.

A new asylum was about to open in 1867 at the farm of St. Anne. Two positions of physician-in-chief were created there: one was given to Prosper Lucas; the other was offered to Dagonet. Dagonet did not leave the Asylum of Stephansfeld and the faculty of Strasbourg without regret, but he would certainly have hesitated to accept his new functions had he been able to anticipate the difficulties that awaited him there. Christian[4] relates that "the sweet, peaceful, conciliatory man, was obliged to fight against some ferocious adversaries . . . . He fought since he was forced to fight and because he had right on his side. He won out in the end."

In 1868 the Medical Psychological Society dedicated several sessions to the discussion of the dangerously insane. According to Dagonet the protection of the higher interests of society is a question about which doctors are not able to make judgments; they are not obliged to consider the seriousness of the act itself and must in case of recovery encourage the patient's discharge while recommending, in case of the onset of an imminent relapse, immediate reinstitutionalization. For epileptics he considered it necessary to involve the families in attentive supervision after each crisis. "It is repugnant to me," he said, "to accept the opinion . . . , that an insane person who has committed a serious crime should be kept for his whole life in an insane asylum. The law doesn't indicate anything like that and we should not substitute our authority for that of the law." He cited the example of a patient, one who had murdered his wife and children, whom he had found in 1850 in the asylum of Stephansfeld and who, after his complete recovery, was kept for 20 years in the asylum, since the inhabitants of the community opposed his discharge. Freed by German authorities, he remarried and, 25 years after his first crime, again killed his wife and their young children and then committed suicide. Reporting this fact in 1878, Dagonet declared it exceptional and persisted in his opinion, reiterating it in 1882. He was generally opposed to sending all the mentally ill who were called criminals to a special establishment that had the appearance of a prison, and he considered preferable the creation in several asylums of secure quarters where individuals presenting an exceptional form of insanity could be sent.

Without negating the existence of a purely [emotional] insanity, he considered that it was a rare occurrence and that it could

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Address correspondence to Dr Esman, Professor of Clinical Psychiatry, Payne-Whitney Psychiatric Clinic, The New York Hospital-Cornell Medical Center, 525 East 68 St, New York, NY 10021.

not exist for long without being accompanied by intellectual impairment. "All our faculties are in reciprocal dependence and the manifestations of one influence those of the others; . . . the moral sensibility is the habitual stimulant, the exciter, and up to a certain point the regulator of the intellectual functions."

Dagonet distinguished a manic moral insanity, a "lypémanie" [depression] and an impulsive madness. But in these different cases, "the physiognomy which presents the troubles of the moral faculties presents itself with the same characters of excitation, depression, fixicity, perversion and weakness which one can observe for the intellectual functions." [It was this interest in physiognomy that led him to photography as a superior mode of illustration].

The delirium of persecution [paranoia] did not seem to him a particular variety of illness that always has the same presentation and the same evolution. One encountered it in the most diverse forms, dominating in some degree the mental pathology and constituting "a symptomatic group which rests on the same morbid base, that of suffering."

Among its varieties one finds most prominently the systematized delirium of persecution, then the megalomanic form; one encounters it also in stupor, hypochondriasis, mania, senile dementia, general paralysis, and alcoholism. This delirium does not, however, constitute a pathologic state in itself; it may persist throughout life without necessarily being transformed into megalomania and without concluding in dementia, he believed. The description, under the name of "chronic delirium," of a morbid entity which supposedly has a fatal evolution and clearly characterized periods represented, he maintained, an innovation of terminology "which makes the study of mental maladies even more obscure."

The term "stupidité" [stuporousness] seemed to Dagonet poorly chosen and unscientific. He distinguished two forms, the one with complete suspension of the intellectual life [dementia?], the other with suspension of the elementary functions of reasoning and an intense sensorial delirium of a depressive form in which the patient retains his memory [pseudodementia?].

In a discussion of general paralysis in 1887 at the Medical Psychological Society, Baillarger wondered if one should not consider it as a complication or even at times as a consequence of madness. Dagonet responded that in his opinion it was a primary illness, and he discounted the possibility of finding an authentic example of an individual originally suffering from a clear-cut form of mental illness that was followed by general paralysis.

Remembering the times that he spent as a faculty member at Strasbourg, he instituted courses at the Asylum of St. Anne, in which he gave, Magnan reports, "the measure of his vast knowledge, of his erudition, of the penetration of his judgment, of his powerful analytic mind, of his talent of exposition, clear, precise and methodical."

As did many other psychiatrists, Dagonet became the butt of unjustified and absurd attacks, to which he usually would not deign to respond. But in 1881 these insinuations took on an odious character, so much so that the Medical Psychological Society was obliged to reprove them publicly, and to give to their honored colleague the assurance of their esteem.

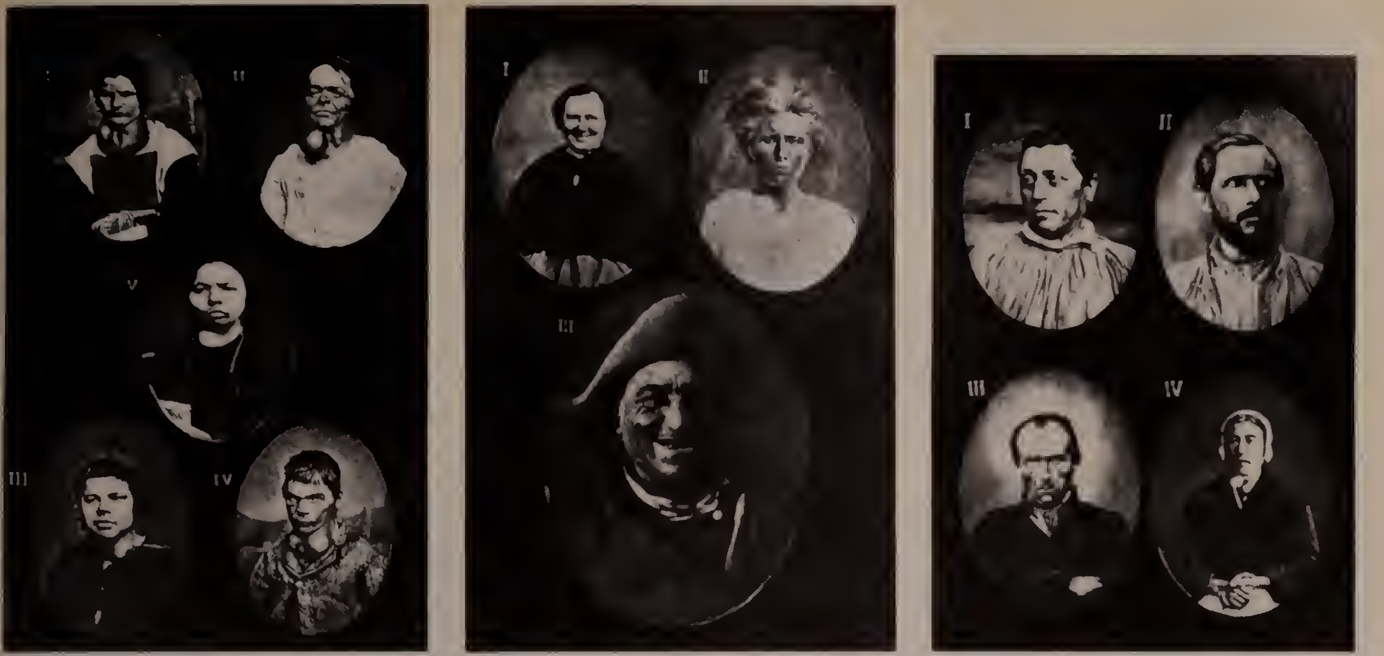
At St. Anne there was an inmate who, having heard talk about a death by strangulation that had taken place on Dagonet's service, invented a tragic story that he confided to a municipal councillor. Without verification, the councillor, with the connivance of the director and without the knowledge of the chief of service (ie, Dagonet), entered a complaint of assassination. The inquiry naturally began to turn, to the confusion of the informers. Meanwhile certain journalists directed violent attacks against Dagonet. He was severely affected but found ardent defenders. "It is necessary that one know without doubt," wrote *Le Progrès Medical*, "if the Director of the Asylum of St. Anne is a man endowed with the flair of a police inspector and the perspicacity of a justice of the courts, or whether he is simply endowed with a disordered imagination and an incurable simplicity. In both cases we demand that he be given a position conforming with his capacities." The director had already left a large Parisian hospital following his claim that abortion and infanticide were being carried out; nonetheless, he had been given the opportunity by the prefectoral administration, thanks to higher-ups, to recover his position; however, he did not remain at St. Anne after this new episode. As for the honorable gentleman who played such an active role in this burlesque scene, he made a specialty of collecting the most implausible stories concerning hospitals and psychiatrists, proving even to disbelievers that monomanias still exist. Tormented by a severe facial neuralgia, Dagonet no longer attended meetings of the Medical Psychological Society. He died on September 4, 1902.

DISCUSSION

Dagonet emerges from this biography as a devoted, nondoctrinaire physician, deeply committed to the French tradition of precise clinical description. His ideas on forensic issues are remarkably modern and, indeed, anticipate current views on the relationship of psychiatry to the criminal justice system. His acuity on clinical matters was considerable; although his diagnostic classifications seem primitive today, it is clear that he was groping toward a system that would do justice to the complexities of clinical data and that would integrate both affective and cognitive disorders into a comprehensive nosology. Thus his grasp, unusual for its time, of the symptomatic, rather than the pathognomic, significance of paranoia, his recognition of the distinct nosologic status of general paresis in its various manifestations, and his willingness to suspend judgment on etiologic grounds. Indeed, in his effort to develop a nosology relatively divorced from theory and resting primarily on a foundation of clinical observation he was not far in spirit from our current nosologists whose Diagnostics and Statistical Manual (DSM III) is yet the latest system which, as Semelaigne[3] says, "gives satisfaction to its authors."

Of greatest interest today, however, are the photographs in the second (1876) edition of Dagonet's book.[1] Chosen from his own collection and from those of colleagues, they are not only the first to appear in a psychiatric text but represent, according to Dagonet himself, "the first application of photograving to medical illustration (p. iv)." In his reviews of the book, Christian[4] said, "These remarkable portraits show all the benefit one may derive from photography, which M. Dagonet was one of the first to introduce when he was at the asylum of Stephansfeld." Along with their captions they reveal much about the nature of psychiatric practice in the mid-19th century. One plate, for example, portrays five individuals with cretinism and massive goiters (Fig, left). Dagonet's lengthy discussion of this disorder suggests its prevalence; it also recalls the persistence of etiologic notions concerning bad air, excess humidity, and impure water, despite his knowledge of the observations of Roulin and Boussingault who had, as early as 1825 and 1831, demonstrated the prophylactic value of iodized salt. Dagonet reflected the general belief that iodine owed its effect to its ability to purify drinking water.

The cases of depression ("lypémanie," Fig, center) are described in the accompanying captions as profoundly psychotic, with multiple hallucinations and delusions of persecution; their diagnostic status by current criteria would be open to some question. On the other hand, the patients with "manie" all look, and are described, in terms that fulfill current criteria for mania (Fig, right).



Left, Patients with cretinism and goiter. Center, "*Lypémanie*," profoundly psychotic cases with multiple hallucinations and delusions of persecution. Right, patients who would fulfill current criteria for mania.

Physiognomy, as exemplified by Dagonet's photographic presentations, represented one failed effort in the struggle to achieve at least descriptive exactitude; DSM III is the latest. Dagonet was truly one of the pioneers, not only of a scientific psychiatry, but also, through his forensic interests, of a humane psychiatry.

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INSANITY AS A DEFENSE IN CRIMINAL CASE

In some jurisdictions a rule has been adopted giving an interpretation to the insanity defense to include cases of so-called "irresistable impulse." Such cases are cases where the defendant although he knows that the act he commits is wrong, does the act under some insane delusion which prevents him from choosing between right and wrong. The law in this State, however, does not accept the said doctrine. It is expressly dealt with by Section 34 of the Penal Law which reads as follows:

"A morbid propensity to commit prohibited acts, existing in the mind of a person who is not shown to have been incapable of knowing the wrongfulness of such acts, forms no defense to a prosecution therefor."

The propriety of the New York rule can well be appreciated in the light of the following statement made by the Court of Appeals in one of the leading cases on the subject:

"We are asked in this case to introduce a new element into the rule of criminal responsibility in cases of alleged insanity, and to hold that the power of choosing right from wrong is as essential to legal responsibility as the capacity of distinguishing between them; and that the absence of the former is consistent with the presence of the latter. The argument proceeds upon the theory that there is a form of insanity in which the faculties are so disordered and deranged that a man, though he perceives the moral quality of his acts, is unable to control them, and is urged by some mysterious pressure to the commission of acts, the consequences of which he anticipates but cannot avoid.

"Whatever medical or scientific authority there may be for this view, it has not been accepted by courts of law. The vagueness and uncertainty of the inquiry which would be opened, and the manifest danger of introducing the limitation claimed into the rule of responsibility, in cases of crime, may well cause courts to pause before assenting to it. Indulgence in evil passions weakens the restraining power of the will and conscience; and the rule suggested would be the cover for the commission of crime and its justification. The doctrine that a criminal act may be excused upon the notion of an irresistible impulse to commit it, where the offender has the ability to discover his legal and moral duty in respect to it, has no place in the law."

The possibilities of unjust results from these general rules may at once be suggested, but the wisdom of these rules can hardly be questioned. The courts too frequently encounter faked defenses of insanity, and must be equipped with harsh remedies to apply when required. The juries are in the final analysis the triers of the facts, and, it is safe to say, very few truly insane persons are unjustly caused to suffer for crimes committed by reason of their insanity.

—LORENZ J BROSNAN, Esq
Insanity as a Defense in Criminal Cases.
NY State J Med 1933; 33:166.

Single lung transplantation in paraquat intoxication

STEPHAN KAMHOLZ MD, FRANK J. VEITH MD, FRED MOLLENKOPF PA-C, CHERYL MONTEFUSCO PHD, SANDRA NEHLSEN-CANNARELLA PHD, RONALD KALEYA MD, KENNETH PINSKER MD, VIVIAN TELLIS MD, ROBERT SOBERMAN MD, LEONARDA SABLAY MD, ARTHUR MATAS MD, MARVIN GLIEDMAN MD, JAMIE GOLDSMITH RN, STANLEY FELL MD, RICHARD BRODMAN MD, AVRAHAM MERAV MD, ARYEH SHANDER MD, INGRID HOLLINGER MD, HIDEO NAGASHIMA MD

Severe, acute lung damage frequently results after ingestion of the herbicide, paraquat* (PQ).[1] Respiratory failure is the major cause of death in PQ-poisoned patients surviving more than 48 hours after ingestion.[2] Prior to 1982, single lung transplantation had been performed on two occasions for patients with terminal respiratory insufficiency due to PQ toxicity.[3] This report describes a patient in whom single lung transplantation was performed after removal of PQ.

CASE REPORT

On August 30, 1982, a 25-year-old man accidentally ingested a small quantity of PQ. He was admitted to the intensive care unit of his regional university teaching hospital on September 5, 1982. Resting dyspnea was present and bilateral alveolar infiltrates were noted on admission chest roentgenogram. PQ nephrotoxicity was manifested by a serum creatinine level of 11 mg/dL. Activated charcoal hemoperfusion[4] was instituted to remove circulating PQ. Hemodialysis was performed because of renal insufficiency and oxygen was administered by Venturi mask.

Despite therapy, the patient's respiratory status continued to deteriorate, and on September 13, 1982 he was transferred to Montefiore Medical Center as a potential candidate for lung transplantation. Soon after admission, endotracheal intubation was required. Arterial blood gases on assisted ventilation (fraction of inspired oxygen [FiO_2] 0.5, tidal volume 1,100 mL, positive end expiratory pressure [PEEP] 10 cm H_2O, rate 20 breaths/min) were pH 7.51; $PaCO_2$ 37; PaO_2 47. Pulmonary artery pressure was 33/16 torr, wedge pressure 14 torr, and thermodilution cardiac output was 15.7 L/min. Activated charcoal hemoperfusion was continued intermittently with filtration cartridges (Adsorba 300, Gambro Corp, West Germany) at flow rates up to 200 mL/min. Over the next 11 days, pulmonary infiltrates progressed (Fig 1A) and respiratory gas exchange deteriorated. On September 24, 1982, arterial blood gases (FiO_2 1.0, tidal volume 1,000 mL, PEEP 11 cm H_2O, rate 46 breaths/min) were pH 7.43; $PaCO_2$ 45, and PaO_2 48. Pulmonary artery pressure had risen to 85/25 torr with a wedge pressure of 16 torr and a cardiac output of 9.0 L/min. Serum and muscle PQ levels had declined to the nontoxic range. On September 24, 1982, left lung allotransplantation was performed utilizing previously described techniques.[5] The donor organ was obtained from a brain-dead, 18-year-old man of compatible size with ABO blood type. Immunosuppressive therapy included cyclosporine (Sandoz, Inc), azathioprine (1.5 mg/kg/day for the first 14 days only) and corticosteroids. The immediate postoperative period was characterized by transient alveolar infiltrates in the allografted lung (Fig 1B) due to the reimplant response.[6] Several episodes of probable allograft rejection occurred (on postoperative days 9, 19, 33, and 45). These were characterized by the rapid onset of new infiltrates in the transplant (Fig 1C), increased pulmonary artery pressures, increased shunt fraction, and by increased number of polymorphonuclear leukocytes on microscopic examination of sputum. These manifestations, attributed to episodic rejection, improved within several hours (Fig 1D) after therapy with high-dose intravenous methylprednisolone (1,000 mg daily × 3 doses).

On the 16th day after transplantation, a right pneumonectomy was performed because of the development of multiple *Pseudomonas* abscesses in the patient's remaining PQ-damaged lung (Fig 1E). After pneumonectomy, arterial blood gases on assisted ventilation (FiO_2 0.35, tidal volume 950 mL, PEEP 0 cm H_2O, rate 18 breaths/min) were pH 7.43; $PaCO_2$ 39; PaO_2 92, and pulmonary artery pressures had returned to almost normal levels (pulmonary artery pressure 32/11 torr, wedge 11 torr, cardiac output 7.1 L/min).

On November 3, 1982 (23 days after right pneumonectomy) a 2-mm bronchopleural fistula developed at the most medial portion of the right bronchial stump. Operative repair via a right thoracotomy consisted of oversewing the bronchial stump and reinforcement with a vascularized, intercostal muscle bundle graft. After surgery the patient was managed with high-frequency jet ventilation (obtained from Memorial-Sloan Kettering Cancer Center, New York City) to minimize mean airway pressures and promote healing of the right bronchial stump.[7] Despite intensive antibiotic therapy for persistent *Pseudomonas* infection, the right bronchopleural fistula reopened eight days after operative repair and the patient died of respiratory failure two days thereafter (seven weeks after transplantation). Histologic sections of the allografted lung obtained at postmortem examination revealed scattered areas of focal interstitial fibrosis and patchy bronchopneumonia without evidence of allograft rejection. The patient's clinical course is shown in Figure 2.

DISCUSSION

In this patient, vigorous and repetitive activated charcoal hemoperfusion treatments prior to lung transplantation were essential to diminish body stores and preclude PQ damage to the lung allograft. We confirmed that adequate removal of PQ had indeed been achieved by serial measurement of serum PQ levels and by determination of PQ tissue stores (determined by analysis of a right rectus femoris muscle biopsy) performed two days prior to transplantation. Both

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From the Departments of Surgery, Medicine, Anesthesiology, and Pathology, Montefiore Medical Center Albert Einstein College of Medicine, The Bronx, New York.

Presented at the January 26, 1983 meeting of the New York Transplantation Society.

This work was supported in part by the James Hilton Manning and Emma Austin Manning Foundation, and by NIH-NHLBI Program Project Grant HL17417.

Address correspondence to Dr Kamholz, adjunct physician, Division of Pulmonary Medicine, Montefiore Medical Center, 111 East 210th St, Bronx, NY 10467.

* 1,1′-dimethyl-4,4′-bipyridylium dichloride

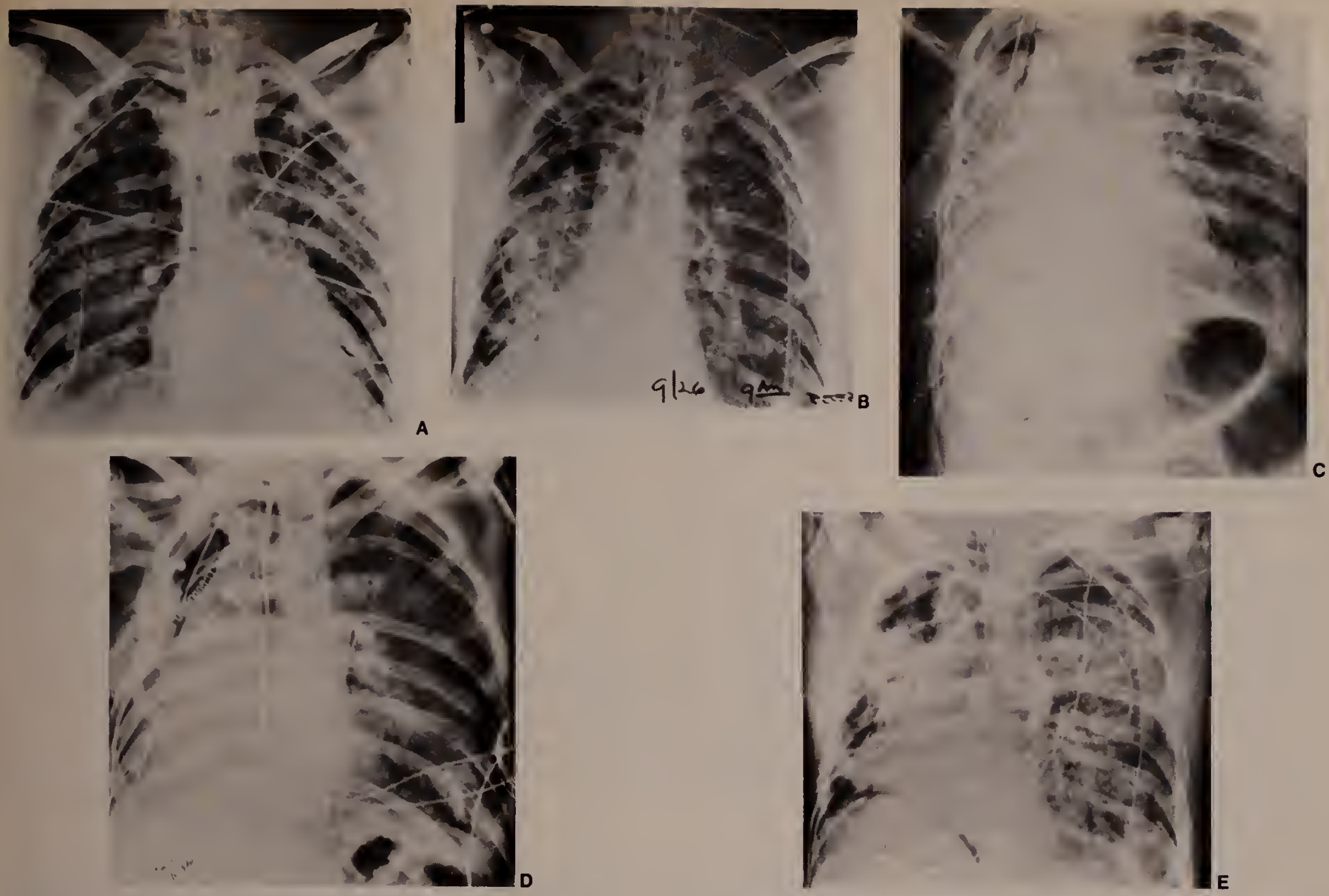

FIGURE 1. Chest roentgenograms of lung transplant recipient. (A) Pretransplant chest radiograph 9/24/82: Bilateral diffuse alveolar infiltrates with multiple cystic lucencies. (B) Posttransplant chest radiograph 9/26/82 shows fully expanded left lung allograft in place. Vascular clips around left hilar structures. Minimal left lower lobe infiltrate due to pulmonary reimplant response. (C) Posttransplant chest radiograph 11/9/83: Diffuse left lung infiltrate due to fourth episode of allograft rejection occurring on the 45th posttransplant day. Note that patient also underwent right pneumonectomy. (D) Posttransplant chest radiograph 11/10/82. Note dramatic clearing of infiltrate in left lung after treatment for allograft rejection (compare 1C). (E) Posttransplant chest radiograph 10/10/82. Note marked consolidation, cavitation, and pneumothorax on right. This radiograph obtained prior to right pneumonectomy.

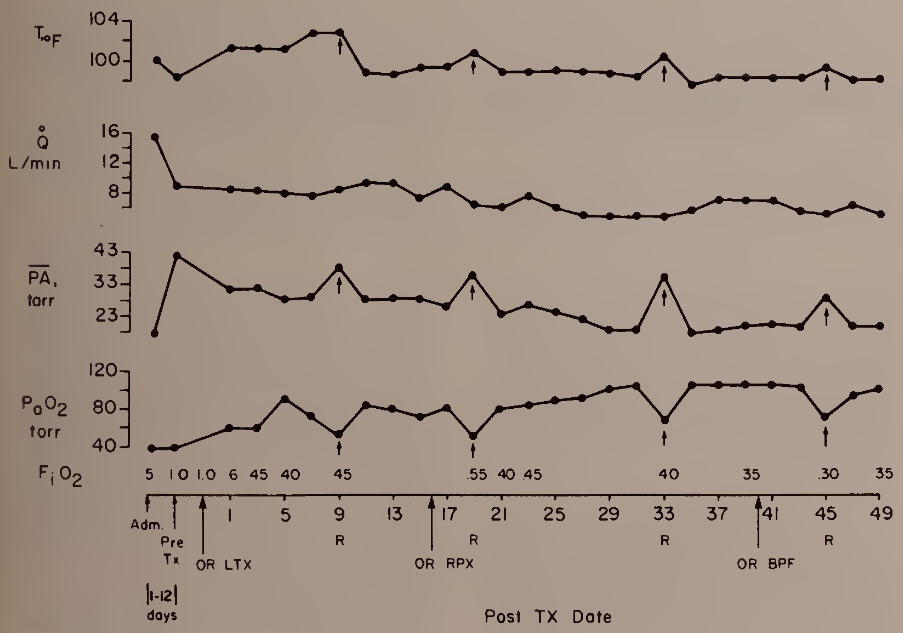

FIGURE 2. Clinical course of lung transplant recipient.

T°F = Rectal temperature, degrees Fahrenheit.

Q̇ L/min = Cardiac output, liters per minute.

$\overline{PA}$, torr = Mean pulmonary artery pressure, torr.

P_aO_2 torr = Arterial oxygen tension, torr.

F_iO_2 = Fractional inspired oxygen concentration.

Adm. = Date of admission to Montefiore Medical Center.

Pre Tx = Immediate pretransplant measurements.

OR LTX = Operating Room for left lung transplant

R = Episode of probable allograft rejection. Small arrows adjacent to curves indicate changes occurring at times of rejection episodes.

OR RPX = Operating Room for right pneumonectomy.

OR BPF = Operating Room for repair of bronchopleural fistula at right pneumonectomy stump.

Post TX Date = Post transplant date. Numbers 1 through 49 on horizontal axis correspond to dates.

patients receiving lung transplants because of PQ toxicity prior to 1982 probably sustained severe PQ damage to the transplanted lung, although they may also have had allograft rejection.[8]

The recent introduction of the potent immunosuppressive agent cyclosporine has increased the success of experimental lung[9] and clinical heart-lung allotransplantation.[10] We utilized this drug as the major immunosuppressive agent in this patient. Unfortunately, frequent episodes of probable allograft rejection occurred nonetheless. It is possible that these rapidly developing infiltrates, accompanied by hemodynamic and gas exchange abnormalities, may have been due to ongoing *Pseudomonas* bronchopneumonia. However, the abruptness of onset of improvement after administration of intravenous methylprednisolone suggests that the etiology was indeed allograft rejection, despite the lack of histologic documentation (see Fig 2). Although these episodes and the resultant requirement for large doses of corticosteroids occurred despite the use of cyclosporine immunosuppression, we were encouraged by the complete healing of the transplant bronchial anastomosis and the absence of rejection in the allografted lung at postmortem examination.

Persistent *Pseudomonas* bronchopulmonary infection, high-dose methylprednisolone therapy, and the need for continued assisted ventilation as a result of frequent rejection episodes may have contributed to poor healing of the right bronchial stump. This complication was responsible for intractable ventilatory failure and led to the patient's death.

This patient's course suggests that (1) a single, transplanted lung can provide adequate pulmonary function with relatively normal pulmonary artery pressures; (2) the bronchial anastomosis of a single lung transplant can heal adequately; (3) episodes clinically compatible with lung allograft rejection occurring during cyclosporine immunosuppression can be recognized and reversed; and (4) single lung transplantation utilizing cyclosporine immunosuppression may be considered as a possible therapeutic intervention for patients with terminal respiratory failure due to acute PQ toxic pneumonitis.

Acknowledgments. The invaluable assistance of Cole Ray, RRT and Jeffrey S. Grover, MD of Memorial-Sloan Kettering Cancer Center is greatly appreciated. In addition, we wish to express our thanks to George Tanis and Barry Mordin for their artistic and photographic expertise, and to Steven Levine for manuscript preparation.

Editor's Note. One of the major problems hampering the progress of single lung transplantation has been the lack of suitable lung donors. Several factors account for this scarcity, including contamination of the lungs during or after the cerebral insult leading to brain death, lack of awareness or cooperation on the part of physicians caring for potential organ donors, and family resistance to organ donation. General awareness of the optimal methods of caring for potential organ donors to maximize the possibility of multiorgan transplantation can help to increase the likelihood of successful single lung transplantation in the future. Increased understanding in the medical community and among the general public will foster these goals.

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Drug-resistant tuberculosis of the hip in a child

LAURA S. INSELMAN, MD, CRISTINA E. DELAVEGA, MD, HUGH E. EVANS, MD

Both extrapulmonary and pulmonary manifestations of tuberculosis are increasing in incidence in certain segments of the population in the United States.[1] Skeletal tuberculosis, particularly of the hip, may show clinical and radiologic findings similar to those of other musculoskeletal disorders in children. We recently encountered a child with tuberculosis of the hip caused by a multiple drug-resistant strain of *Mycobacterium tuberculosis*.

CASE REPORT

A $2\frac{1}{2}$-year-old Hispanic girl had a six-month history of progressive limp and 15 mm of induration on a tuberculin skin test (5TU PPD). Seventeen months earlier her 5TU PPD had 5 mm of induration, and, because of a history of exposure to active tuberculosis from her father, isoniazid therapy was begun. Compliance was poor and a year later her PPD had 10 mm of induration. Isoniazid therapy was again prescribed. A limp subsequently developed, and a well-delineated lytic lesion measuring 1 cm in diameter with a sclerotic rim and central calcification was seen in the left acetabulum on x-ray film (Figure). Her previously normal chest roentgenograms now revealed bilateral patchy lower lobe infiltrates.

The left hip was tender to palpation, and there was limited range of motion of flexion, abduction, adduction, and internal and external rotation. There was no erythema,

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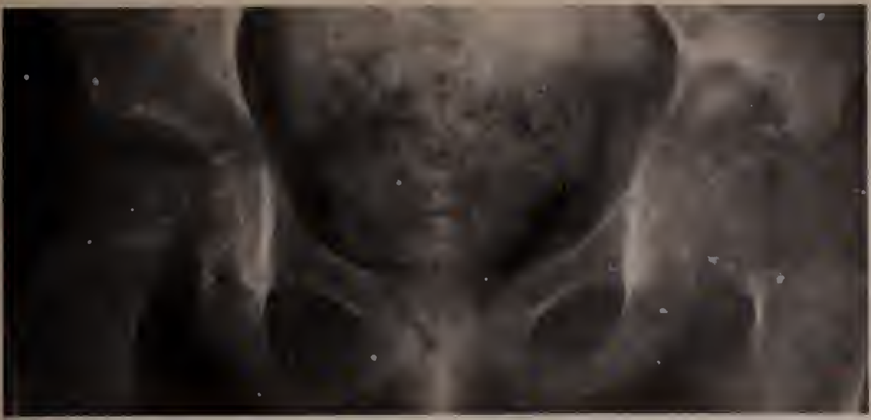
From the Pulmonary Division, Department of Pediatrics, Jewish Hospital and Medical Center of Brooklyn, Brooklyn, New York.

Address correspondence to Dr Inselman, Department of Pediatrics, North Shore University Hospital, 300 Community Drive, Manhasset, NY 11030.



Tuberculous lytic lesion with sclerotic rim and central calcification in the left acetabulum in a 2½-year-old girl.

Drug Resistance Pattern of *Mycobacterium tuberculosis* Isolated from Patient and Father.

Drug	Concentration μ/mL	Patient	Father
Isoniazid	0.2	100*	100*
	1.0	100	100
	5.0	100	100
Rifampin	1.0	50	50
Streptomycin	2.0	100	100
	10.0	100	100
Para-aminosalicyclic acid	2.0	100	100
Ethionamide	5.0	25	0
Ethambutol	5.0	0	0
Cycloserine	30.0	0	0
Capreomycin	10.0	0	0
Kanamycin	5.0	0	0
Pyrazinamide	50.0	0	Not tested

* percent resistance of *Mycobacterium tuberculosis* to drug.

swelling, obvious deformity, increased temperature of the overlying skin, discrepancy between length of legs, or muscle atrophy.

The peripheral WBC count was 15,500/mm^3 with 62% polymorphonuclear neutrophils, 27% lymphocytes, 7% monocytes, and 4% band forms. Hemoglobin was 13.8 g/dL and erythrocyte sedimentation rate was 33 mm/hour. Results of urinalysis, liver function tests, and technetium 99 bone scan of the hips were normal.

After fluid from the hip joint was aspirated, daily therapy with 300 mg each of isoniazid, rifampin, and ethambutol was begun. Acid-fast and Gram stains and bacterial cultures of the aspirated fluid were negative. *Mycobacterium tuberculosis* resistant to multiple drugs grew from the fluid (Table). Triple antituberculous therapy was continued without evidence of toxicity. She was also treated initially with traction and then with hip spica casts for five months. Ten months after starting antituberculous therapy the limp, pain, and tenderness subsided. Range of motion in abduction and internal and external rotation was only mildly limited, and the acetabular lytic lesion and pulmonary infiltrates had decreased. Triple antituberculous therapy is planned for two years.

The patient's 40-year-old father, who did not have diabetes and was not known to abuse alcohol, had primary drug-resistant active pulmonary tuberculosis. The organism from his sputum showed the same sensitivity pattern as that of his daughter (Table). Epidemiologic investigation did not reveal the source of the father's infection.

DISCUSSION

From 1974 to 1981 the reported case rate of tuberculosis under age 15 years in New York City declined from 8.1 to 4.6 per 100,000 population, similar to the trend observed throughout the United States.[2,3] However, an increasing incidence of tuberculosis in both indigenous and immigrant populations throughout the country indicates a possible reemergence of the disease.[1]

During the past few years an increasing proportion of cases of tuberculosis has been identified as extrapulmonary. Fifteen percent of all cases of tuberculosis in the United States and in New York City result from extrapulmonary disease.[2,3] Skeletal tuberculosis represents approximately 9% of these cases.[3] Despite previous reports of a decreasing incidence of skeletal tuberculosis in children,[4] it has increased in the United States from 3.4% of all cases of skeletal tuberculosis in 1976 to 7.5% in 1980.[3] In contrast, although the overall incidence of skeletal tuberculosis in New York City is rising, this is not apparent in children.[2] Our patient is one of two reported cases in a child between 1978 and 1982 in New York City.

In addition, our patient probably had primary drug-resistant tuberculosis. Although this is unusual in children in our hospital,[1] its incidence was approximately 7% for all antituberculous drugs in New York City and the United States in 1980.[2] In the foreign-born populations in the United States its incidence ranges from 12% to 32% and is particularly high under age 10 years.[2,5]

Isoniazid prophylaxis may not be effective in preventing the development of active tuberculosis among contacts of individuals infected with isoniazid-resistant *M. tuberculosis*.[6] Its failure in our patient may also be due to poor compliance. Only isoniazid has been proved effective in prevention of the development of tuberculosis in PPD converters, and it remains the preferred drug for preventive therapy. In cases of exposure to isoniazid-resistant strains of the tubercle bacillus, both isoniazid and rifampin may be used.[7]

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Arterioportal fistula secondary to percutaneous transhepatic cholangiography

SHELLEY NAN WEINER, MD

Fine-needle percutaneous transhepatic cholangiography (PTC) and percutaneous biliary drainage (PTHBD) are widely accepted methods of evaluating and managing patients with obstructive jaundice.[1-5] These methods are generally safe, but complications including hemorrhage, bile leaks, and sepsis have been reported.[2-4] In addition, vascular complications such as intrahepatic artery aneurysms and pseudoaneurysms, hematomas, arterioportal venous fistula, and arteriohepatic venous fistula have been reported to occur secondary to catheter drainage technique.[6,7]

Arterioportal shunts secondary to puncture of the liver with large-bore needles for liver biopsy and cholangiography have also been reported.[8,9]

To our knowledge, four cases of arteriovenous fistulas secondary to fine needle PTC have been reported.[3,10] We recently saw another patient with obstructive jaundice secondary to carcinoma of the pancreas who developed an arterioportal fistula after a fine-needle PTC.

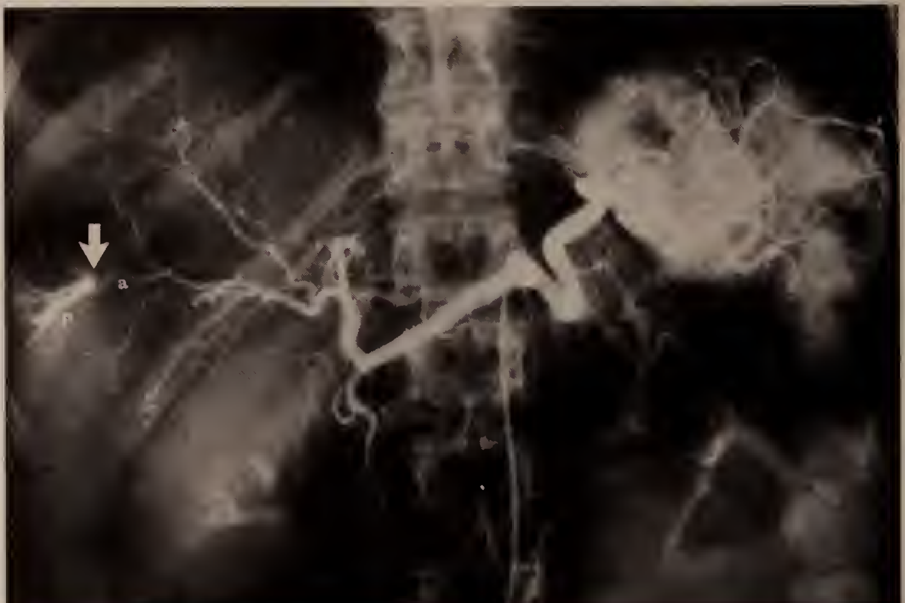
CASE REPORT

A 53-year-old woman came to the general medical clinic of another hospital with a two-week history of vague abdominal pain, indigestion, and increasing jaundice. Physical examination at that time was unremarkable except for generalized icterus. Laboratory evaluation showed total bilirubin, 1.4 mg/dL; alkaline phosphatase, 361 IU/L; SGOT, 193 IU/L; and SGPT, 505 IU/L. She was sent home with a provisional diagnosis of hepatitis but returned one week later with increasing jaundice (bilirubin, 10.8 mg/dL). Screening for hepatitis antigen was negative.

The patient then underwent an abdominal computed tomography (CT) scan which demonstrated dilated intrahepatic and extrahepatic bile ducts, a distended gallbladder, and a mass in the head of the pancreas. Abdominal sonography confirmed these findings.

The patient was transferred to the Hospital of the Albert Einstein College of Medicine for further evaluation. She underwent a fine-needle cholangiogram which showed obstruction of the common bile duct just distal to the cystic duct consistent with a carcinoma of the head of the pancreas. Two passes were made with the needle. Her coagulation profile was within normal limits.

Five days later the patient underwent abdominal angiography for staging prior to surgery. This demonstrated a hepatic artery-portal vein fistula in the right lobe of the liver in the same area where the puncture for the percutaneous cholangiogram had been made (Fig). The hepatic, splenic, and gas-



Top: Selective celiac arteriogram demonstrating arterioportal fistula (arrow); *a* is a branch of hepatic artery, and a branch of portal vein. Bottom: Late phase of arteriogram showing slow washout of small branch of portal vein (*p*) involved in fistula.

From the Department of Radiology, Albert Einstein College of Medicine, The Bronx, New York

Address correspondence to Dr. Weiner, Associate Professor of Radiology, Department of Radiology, Hospital of the Albert Einstein College of Medicine, 1825 Eastchester Rd, Bronx, NY 10461.

troduodenal arteries and the splenic, superior mesenteric, and portal veins were normal.

The following day the patient underwent an exploratory laporatomy. The tumor could not be freed from the transverse mesocolon and a gastrojejunostomy and choledochojejunostomy was performed.

The patient had an uneventful recovery and her liver function returned to normal.

DISCUSSION

The complication rate for fine-needle PTC is low. In a large multi-institutional survey by Harbin et al[3] sepsis was reported in 1.4% of cases, fever without sepsis in 3.4%, intraperitoneal bile leak in 1.45% and hemorrhage and hematoma each in less than 1%. Others have reported a slightly higher incidence of fever and sepsis,[1,2] which is probably related to variations in technique and preprocedural preparation of the patient.

Of the 2,006 cases reported by Harbin there was one arterioportal venous fistula found at angiography three days after a PTC. The patient was asymptomatic. Okuda et al[10] reported three arterioportal venous fistulas after fine needle cholangiography in a series of 79 patients.

Hepatic arteriovenous fistulas (almost always arterioportal fistulas) secondary to liver biopsy have been well documented[8-10] and are usually discovered incidentally at angiography. Most of these are small, peripheral fistulas which are asymptomatic and do not cause portal hypertension. They will usually close spontaneously requiring no intervention.[10]

There is a close anatomic relationship between the portal vein, hepatic artery, and bile ducts in the portal triad. During PTC, the needle may enter branches of the hepatic vein, portal vein, or hepatic artery as well as the bile ducts.

The hepatic veins are distant from the portal triad which explains the relatively low incidence of hepatic artery-hepatic vein fistulas. It is not surprising, however, that as the fine needle punctures the bile duct for a cholangiogram it may also traverse a nearby branch of the portal vein or hepatic artery, or both. This may in turn result in an arteriovenous fistula.[3,10]

Vascular complications of PTC and PTHBD appear to be related to the size of the needle or catheter, or both, with a much higher incidence with the latter technique.[2] Hoevels and Nilsson[6] reported vascular complications in 27 of 83 patients undergoing PTHBD.

Angiography is now being used more frequently in the preoperative evaluation of patients with obstructive jaundice and is often performed a few days after a PTC. Vascular changes secondary to PTC may therefore be seen with increasing frequency. It is important to recognize that most of these fistulas will close spontaneously and are of no clinical significance, as are those seen after a liver biopsy.

Acknowledgment. The author wishes to thank Michael Gold, MD, Department of Surgery, who referred this patient to the Department of Radiology.

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Life-threatening hemoptysis and bronchoesophageal fistula in primary tuberculosis

RICHARD F. LARSEN, MD

Primary pulmonary tuberculosis is the reaction of the previously uninfected host to the tubercle bacillus. The presence of hilar or paratracheal node involvement is the roentgenographic finding that differentiates primary from postprimary tuberculosis, especially in adults where it is usually a minimally symptomatic process.[1] Tracheobronchial involvement confirmed by bronchoscopy has been reported in 28% of children with primary tuberculosis by Weber et al.[2] In its advanced form endobronchial disease is characterized by the presence of caseation and granulation tissue within the bronchus.[3] Bronchoesophageal fistula formation is a rare complication of endobronchial tuberculosis. Only five cases were documented in a 50-year survey at the Mayo Clinic.[4]

The symptoms of endobronchial tuberculosis are generally nonspecific and include dyspnea, wheezing, and a persistent nonproductive cough.[5,6] Tuberculous endobronchitis is generally coincident with extensive parenchymal infiltration but has been reported in the presence of a normal roentgenogram and symptoms of several years' duration.[7] We report a case of primary tuberculosis in an adult with extensive endobronchial involvement presenting as massive hemoptysis and adult respiratory distress syndrome (ARDS), complicated by bronchoesophageal fistula formation.

CASE REPORT

A 24-year-old woman was admitted to the hospital with a six-week history of weight loss,

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From the Department of Medicine, Division of Pulmonary Medicine, Indiana University School of Medicine, Indianapolis.

Address correspondence to Dr Larsen, United States Army Research Institute of Environmental Medicine, Natick, MA 01760.

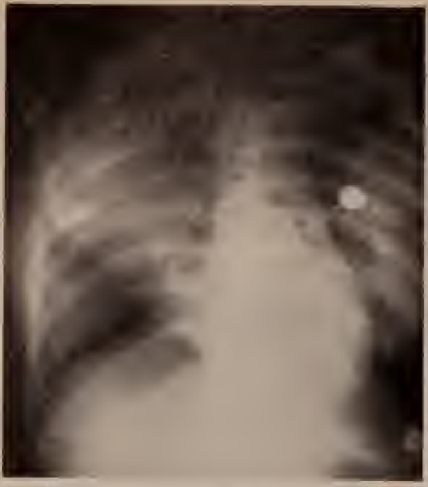

FIGURE 1. Chest roentgenogram six hours after intubation demonstrates new bilateral infiltrates.

fever, cough, pleuritic chest pain, and night sweats. Two weeks before she was diagnosed as having "flu-like syndrome," after a normal chest roentgenogram was obtained. An intimate contact was under therapy for active pulmonary tuberculosis, but the patient had a negative skin test (5 TU PPD) two months before this admission as part of contact surveillance.

On admission, the patient appeared poorly nourished but in no acute distress although she had frequent paroxysms of nonproductive cough. Her oral temperature was 102.8°F., pulse 112, and respiratory rate 20 per minute. Initial laboratory determinations included a WBC count of 13,200 with leftward shift. Platelet count was adequate. Prothrombin time was 4 sec greater than control. Chest roentgenogram on admission demonstrated new bilateral hilar prominence and a patchy right-sided perihilar infiltrate. Sputum Gram's stain and smear for acid-fast bacilli were negative.

Six hours after admission the patient experienced severe hemoptysis. She expectorated more than 400 mL of blood, inhaled some of it, and went into acute respiratory distress. An endotracheal tube was placed and large quantities of fresh blood were suctioned from the tracheobronchial tree. A large-bore nasogastric tube was also placed and fresh blood was evacuated from the stomach.

Acute respiratory failure and ARDS evolved six hours after intubation. Chest roentgenogram demonstrated new bilateral infiltrates (Fig 1). Despite mechanical ventilation and 18-cm H_2O positive-end expiratory pressure (PEEP), arterial blood gases revealed significant hypoxemia: forced inspiratory oxygen (FIO_2), 0.75; pH, 7.45; PaO_2, 57; $PaCO_2$, 34. The pulmonary capillary wedge pressure was 5 mm Hg.

Fiberoptic bronchoscopy two hours after intubation demonstrated friable hemorrhagic mucosa of the right mainstem bronchus extending to the bronchus intermedius. Bilateral blood clots were removed with a rigid bronchoscope. Several smears of the involved bronchial mucosa obtained at bronchoscopy were positive for acid-fast bacilli. Antituberculosis therapy with isoniazid, rifampin, and streptomycin was begun. A Carlen's double-lumen endotracheal tube was placed to control continuing right-sided hemorrhage and prevent further spillover to the contralateral lung.

Esophagogastroscopy revealed a regular tear in the esophageal mucosa at 28 cm with evident air leakage. No site of gastrointestinal bleeding was demonstrated. By the third hospital day hemoptysis had ceased, the Carlen's tube was replaced with a standard endotracheal tube, and PEEP was discontinued. Results of the tuberculin skin test taken on the day of admission showed 15 mm induration at 48 hours.

On day 4 the patient's arterial oxygenation worsened and gastric contents were suctioned from the tracheobronchial tree. Repeat fiberoptic bronchoscopy demonstrated granulation tissue in the right mainstem and bronchus intermedius. Methylene blue instilled in the nasogastric tube rapidly appeared in the right mainstem bronchus. Fifty percent of the inspired tidal volume was entering the gastrointestinal (GI) tract through the widely patent bronchoesophageal fistula. Attempts at decompression with a Blakemore tube were unsuccessful, and significant abdominal distention with impairment of diaphragmatic excursion ensued. To eliminate the influx of gas into the GI tract, a venting procedure was deemed necessary. A diverting cervical esophagostomy with distal esophageal closure was performed. This allowed the large volume of gas passing into the esophagus to escape through the esophagostomy. But despite minute ventilation in excess of 33 L, alveolar ventilation remained inadequate and hypercarbia developed (pH 7.25, PaO_2 57, $PaCO_2$ 55, FIO_2 0.75).

High-frequency positive pressure ventilation (HFPPV) was attempted. A Bear respirator modified with low-compliance tubing was used at a respiratory frequency of 60 per minute, tidal volume of 220 mL, and FIO_2 of 0.75. This improved oxygenation and eliminated air leakage, but after 40 minutes of therapy HFPPV was discontinued because of an increase in $PaCO_2$ of 10 mm Hg (pH 7.20, PCO_2 65, PaO_2 67). Standard ventilator management and frequent position changes to minimize air leakage were reinstituted.

The clinical course was further complicated by *Candida* septicemia, requiring 1.5 g amphotericin B, and *Pseudomonas aeruginosa* pneumonitis and empyema, which was treated with antibiotics and chest tube drainage. The endotracheal tube was removed on day 56 and the patient was discharged two weeks later.

Cultures from bronchial washings performed on the first day proved to be positive for *Mycobacterium tuberculosis* sensitive to all antibiotics commonly tested. Chest roentgenogram two months after discharge showed bilateral fibrous residua (Fig 2). Two and one half months after discharge, the patient was admitted again and a right thoracotomy was performed. A fistula was demonstrated between the right mainstem bronchus and the esophagus. Dense adhesions were present in the area of the right hilum. A 4-cm paratracheal lymph node removed at this time revealed chronic granulomatous inflammation, but culture of this material yielded neither mycobacteria nor fungi.

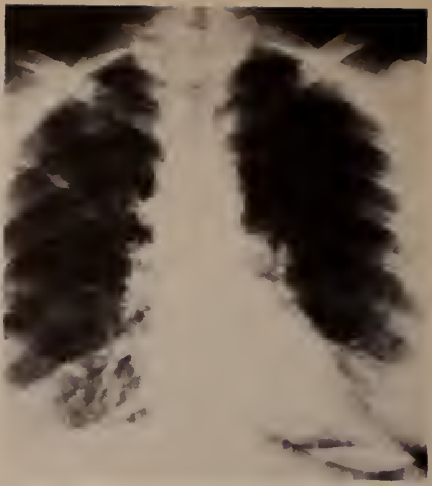

FIGURE 2. Two months after discharge. Bilateral fibrous residua are present.

DISCUSSION

The endobronchial disease observed on fiberoptic bronchoscopy resulted in life-threatening hemoptysis and aspiration progressing to ARDS. In a series of routine bronchoscopies of adult patients with active pulmonary tuberculosis, an 11% incidence of tracheobronchial involvement was reported.[8] Only 50% of these patients had any symptoms referable to the airways, and hemoptysis was not reported. Tuberculosis was the most common cause of life-threatening hemoptysis in a series of 67 patients, but in all cases there was extensive cavitary disease, advanced tuberculous bronchiectasis, or post-tuberculous mycetoma.[9]

The evolution of the bronchoesophageal fistula was complex. The endoscopically visible laceration of the esophagus at the level of the right mainstem bronchus implicates the placement of the nasogastric tube as the precipitating event. Lesions of this nature may produce mediastinitis secondary to bacterial contamination. In our case the nasogastric tube perforated the esophageal wall and adjacent bronchus. This was confirmed at the time of esophagogastroscopy on day 1 by air leakage coincident with tidal volume ventilation. Extensive tissue necrosis and inflammation due to primary tuberculous endobronchitis allowed the bronchus to be more easily penetrated, a normally unexpected occurrence in esophageal lacerations of this type.

The high intrapulmonary pressure needed to ventilate our patient was a direct consequence of ARDS. The bronchoesophageal fistula presented less resistance to airflow than did the patient's poorly compliant lungs. The cervical esophagostomy and distal esophageal closure were intended only to divert the large volume of gas entering the GI tract. The source of abdominal distention was relieved by the venting procedure, but the magnitude of wasted ventilation continued as expected, prompting the trial of HFPPV. This technique uses small tidal volumes, often below the patient's physiologic dead space, and rapid respiratory frequencies, and allows lower peak airway pressures. HFPPV has decreased air leakage in bronchopleural fistula, and has been reviewed by Sjostrand.[10,11] Conventional ventilators can be modified to perform HFPPV.[12] In our patient, adequate arterial oxygenation was maintained and air leakage decreased with HFPPV, but because of an increase in $PaCO_2$ we had to discontinue therapy. Recent evidence suggests that respiratory frequencies of 200 per minute or greater are most effective in eliminating carbon dioxide.[13]

In conclusion, primary tuberculosis endobronchitis should be considered in the differential diagnosis of hemoptysis. Reliance on expectorated sputum samples may be inadequate and fiberoptic bronchoscopy with appropriate smears and cultures may be the diagnostic modality of choice. Clinicians should be alert to the possibility of iatrogenic complications, especially involving instrumentation of the esophagus and tracheobronchial tree.

Acknowledgments. The author wishes to thank Sam Bedsole, RRT, for his technical assistance in the institution of HFPPV, Robert B. Stonehill, MD and Praveen N. Mahur, MD for their valuable criticism, and Jeanne Davis for preparing this manuscript.

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FROM THE LIBRARY

AN APPRAISAL OF PRESENT DAY METHODS OF RAISING CHILDREN

Despite all the wonderful advances in the medicine of childhood, I believe that the youngsters of the older time were possibly better human specimens, both physically and mentally, because they were not exploited by the efficiency expert and commercialist; they were not deprived of their vitamins by a machine age and supplied them unintelligently by the over-zealous; they were not stuffed to the distressing point because someone had misinterpreted the calorie and they were not on a mass production basis, required to meet specifications. . . .

The children of today, then, are at the mercy of the masses led by over-zealous and unthinking setters of fashion. Although I make my living in the practice of pediatrics I honestly believe that they deserve a certain amount of protection from the pediatrician, the nutrition worker and the psycho-analyst, as well as from the propagandist and the exploiter, and should be permitted to live a rational and not too carefully guarded existence, which may be summed up to include three simple meals daily, the discouragement rather than the encouragement of the bite between meals, the withdrawal of food when the appetite is lost rather than its forcing in a misdirected effort to improve nutrition, plenty of time for exercise in the open air and school hours adjusted to play, outdoor living and meals rather than the reverse as is now the case. Let us forget the weight chart and estimate physical and mental development by the general appearance of well-being, the disposition or reaction to surroundings, the susceptibility to fatigue and to infections and by the progress up or down the physical scale.

The obligation of the pediatrician and of the general practitioner should be to prevent overdoing, unnecessary and unwarranted treatment, to stand between the child and the over enthusiastic specialist, whether lay or medical, to see to it that in their efforts to justify their specialties they do not swing the pendulum to the breaking point.

I am sorry that I can not agree with Dr. Hutchinson in his criticism of the periodic health examination. I am sure that, in the case of the child at least, many conditions, if found early enough, may be corrected, although it is very probably true that there is a great deal of nonsense about the beginnings of disease in adult life and that many of them can not be detected early and if detected can not be cured. Periodic examinations in infancy or early childhood are often worth while if for no other reason than to assure a mother whose nervousness and worry may distinctly react upon the child.

FRANK VAN DER BOGERT, MD

An Appraisal of Present Day Methods of Raising Children
NY State J Med 1931; 31:343.

NYJ NEWS FEATURES

State-owned genetic engineering company seeks private investors

Virogenetics, a biotechnology company set up in 1981 by New York State's Department of Health, is negotiating with private investors who may provide both the capital and business expertise needed to market vaccines for herpes and hepatitis B that were genetically engineered by health department researchers.

The company, headed by Health Commissioner David Axelrod, MD, is a for-profit enterprise that will hold patent rights for the process of genetically engineering the vaccinia vaccines. The initial development of the process was accomplished by Enzo Paoletti, PhD, and Dennis L. Panicali, PhD, of the health department's Center for Laboratories and Research in Albany.

Virogenetics is a subsidiary of Health Research, Inc, an Albany-based company set up by the health department 30 years ago to attract money from corporations and the federal government to support the department's activities. Projects that have received such funding include studies of the health effects of overhead power lines and genetic screening programs.

Getting Down To Business

The vaccinia technology will not be marketed by the health department itself, according to Michael Barth, executive director of Health Research, Inc. Mr. Barth told the *Journal* that one option was to have either a pharmaceutical investor or venture capitalist come in and fund the corporation.

"We would put up the technology for our share of the corporation," he said. "The corporation would proceed to develop the technology."

The other approach, which would be pursued if Virogenetics doesn't get off the ground, is for Health Research, Inc to offer licenses for the patent to pharmaceutical companies. Right now, the Virogenetics option is more attractive to the health department because it would ensure that economic development of these products would occur in New York State, according to Peter Slocum, Director of Public Affairs for the New York State Department of Health.

"You'll create hundreds of jobs eventually, to produce this in Albany," "If you license this to 'ABC Drugs' in Phoenix, Arizona, the jobs are going to end up in Phoenix, Arizona."

Mr. Barth said that there had been no criticism of the health department's plan to involve state workers in a company funded by private investors. Of primary concern to the department, was getting the technology out.

"The way to do that," he said, "is to attract private capital, because it is going to take many, many millions of dollars to get this through the various regulatory processes and to finish the basic research. But the big cost is going to be getting it through the regulatory process. And that's something that we feel is best done in the private sector."

Genetic Cut And Paste

In order to produce the genetically engineered vaccinia viruses, which have heretofore been used for smallpox vaccine, Drs Panicali and Paoletti isolated the genes for the herpes virus glycoprotein D and hepatitis S antigens. The herpes or hepatitis antigen gene was then inserted into a portion of the vaccinia DNA.

"What we generate," Dr Panicali told the *Journal*, "is a piece of DNA which has vaccinia DNA sequences at either end, and in the middle, flanked by the sequences, is a foreign DNA."

The researchers infected various tissue culture cells (human, monkey, and chick embryo) with the unaltered vaccinia viruses. They then added to the infected cells the genetically engineered pieces of DNA containing either hepatitis or herpes antigen genes. The pieces of vaccinia DNA flanking the foreign insert then combined with the homologous vaccinia DNA sequences, bringing with them the foreign DNA. The previously unaltered vaccinia virus DNA segments thus acquired herpes or hepatitis antigen genes. The viruses then replicated in the cell as usual, and were subsequently isolated. The vaccinia virus, though genetically altered, retains its ability to elicit an immune response to smallpox in experimental animals.

Future Possibilities

Dr Panicali said that the basic technique for genetically altering the vaccinia virus was flexible enough so that more than one foreign gene can be inserted into the vaccinia genome.

"We can create a virus that contains the antigen for both hepatitis and herpes virus, so one virus would elicit immune response to both of those diseases."

There are no plans for doing that yet, because a great deal of animal testing remains to be done with the vaccinia technology. How long it will take before tests of the vaccinia virus begin on humans depends on the progress made on animal studies designed to demonstrate the efficacy and safety of the vaccines.

"We anticipate it will probably be about three years," Dr Panacali said. "But that's more guess than scientific expertise."

Mr Barth, of Health Research, Inc, said that the process of genetically engineering vaccinia viruses may eventually also be used for gene therapy. But that is many years off, and in the meantime Virogenetics will stick with developing the vaccinia technology until it is ready for testing in humans.

NYJ NewsFeatures is compiled and written by Marc Kusinitz, PhD

Insurance coverage for treatment of alcohol dependence highlights need for qualified counselors

A New York State law requiring health insurance companies to cover treatment of people suffering from alcohol dependence will go into effect September 1.

The law, chapter 595 of the laws of 1983, requires that all health insurance contracts initiated or renewed on and after that date must provide for 60 days of outpatient visits by victims of this disease to clinics accredited by the Division of Alcoholism and Alcohol Abuse Services or by the Joint Commission on Accreditation of Hospitals. Twenty of those days can be used by members of the patient's family for counseling. Insurers cannot deny coverage when the patient receives treatment at an accredited institution.

The requirement that the institution must be accredited reduces the likelihood of charlatans setting up shop to cash in on the new law. One of the health professionals who had been concerned that such abuses might take place without such safeguards is Ann D Wright, Director of Alcohol Services at Four Winds Hospital, an 80-bed facility in Katonah, NY that sets aside 20 beds for people with alcohol dependence.

"It's just like Medicaid," she told the *Journal*. "Remember what happened? Everybody set up a nursing home."

But according to Madeline Lewis, Public Information Coordinator of the Division of Alcohol and Alcohol Abuse Services, which oversees more than 465 treatment facilities, the state's supervision of the field of counseling should prevent major abuses. She emphasized instead the benefit of this bill, saying that it will "increase the likelihood of people getting early treatment. And the more early intervention there is, the better success there is for treating the disease."

> *"The more early intervention there is, the better success there is for treating the disease."*

"It's a recognition in the pocketbook that one needs to get treated for this and get reimbursed for it," she added.

She said that the professionals in the field strongly support the law because it legitimizes alcohol dependence not only as a disease, but also as a family disease.

Treatment of the disease requires a multidisciplinary approach that depends on a team of health professionals. Sheila B. Blume, MD, the former director of the Division of Alcoholism and Alcohol Abuse Services, speaking before the New York Academy of Medicine in May 1982, emphasized this point in her description of the treatment as a multistep process: identification, intervention, detoxification, rehabilitation, and long-term follow-up (*Bull NY Acad Med* 1983;59:171–180). Emphasizing the need to target therapies to appropriate disease stages, she pointed out that psychotherapy and vocational rehabilitation, for example, are very effective during treatment. But they are "perfectly useless when applied before appropriate problem identification and detoxification are complete."

Credentials For The Counselors

The recognition that treatment of alcohol dependence requires a multidisciplinary approach and a thorough understanding of the disease process and its stages, as well as its physical, psychological, and social aspects, prompted the formation of a professional organization of counselors in 1976. According to Charles Peckham, executive director of the New York Federation of Alcoholism Counselors (NYFAC), there was really no organized, formal training of alcoholism counselors even into the 1970s.

"There was no way of determining who had alcoholism knowledge and counseling skills," he said. "The perception was that most of the people with skills and knowledge were recovered alcoholics."

Mr Peckham, who describes himself as a recovered alcoholic, said that there was turmoil at that time between those counselors who were recovered alcoholics and those who were not, because of their different perspectives on the disease and how best to treat it. To bring order to the field, the Division of Alcoholism and Alcohol Abuse arranged a meeting of counselors from around the state. The two-day meeting, held in Albany in February 1976, laid the groundwork for the establishment of NYFAC. Today, NYFAC represents over 70 organizations across the state, including the New York chapter of the National Black Alcoholism Council and the New York State Coalition for Children from Alcoholic Families.

"We have contracted with the New York State Division of Alcohol and Alcohol Abuse Services to be the credentialing agency," Mr Peckham said. "The credential is the only official recognition of alcoholism-based knowledge and counseling skills. In essence, the process attempts to identify competency."

Mr Peckham said that the new insurance law provides for reimbursement to such professionals as physicians, and psychologists and registered nurses with specialized training, and a new category of counselor called the credentialed alcoholism counselor, or CAC. While restricting reimbursement to qualified personnel, or to institutions employing them, the law does not prevent unqualified counselors from collecting directly from uninsured patients.

"There is no requirement to be credentialed in order to work in the field," Mr Peckham told the *Journal*.

To qualify for that credential, a CAC candidate must first take 450 hours of education and training in basic psychology, human growth and development, counseling techniques, and related content. Following completion of this course work, there is a specialized requirement of at least 150 hours of alcoholism-specific training. Candidates must also be able to document a year of supervised work experience.

"That's looked upon as a 35-hour work week, 48-week year," said Mr Peckham. "So we're talking about at least 1,680 hours of work experience as well."

Following satisfactory evaluation of that experience by reviewers who are credentialed counselors, the candidate takes oral and written examinations. Finally, the candidate's portfolio of coursework grades, experience, oral and written examinations, and evaluations is reviewed by the credentials board of the New York State Division of Alcoholism and Alcohol Abuse Services, which makes the final recommendation to the director of the division for approval or disapproval of the credential. The holder of the credential is identified as a qualified health professional by the insurance law. Although an integral part of a treatment facility's interdisciplinary team, CACs are prohibited by the law from setting up a private practice.

A GROWTH INDUSTRY

Mr Peckham emphasized the need for professionals trained specifically to counsel victims of alcohol dependence, in order for the insurance law to be effective. He said that someone with "nice counseling skills and practicing a philosophy that is oriented toward working with someone who is not drug-affected, is not effective. In the early process of recovery, that involvement with alcohol in all its ramifications—physical, psychological, and social, has to be taken into consideration. If you don't do that, the alcoholic gets that message as well, and cannot hear you. Then there are problems of catching up socially and intellectually with one's life. This requires special counseling skills."

There appears to be no shortage of people willing to undergo the training necessary to gain those skills.

"There are so many going into the field now," said Ann Wright, "those jobs are hard to come by."

The counselors who do secure a job find themselves on the front lines of a war against a disease whose cost is enormous. According to Madeline Lewis, the total cost of alcohol dependence to New York State each year in lost jobs, medical expenses, and other costs comes to $4 to $5 billion. Mr Peckham, though offering no estimate himself, called that figure conservative, considering that the total figure for the nation is $120 billion. That figure comes from a recent Congressional report commissioned by the Health Subcommittee of the Senate Finance Committee and carried out by the Office of Technology Assessment.

The war is particularly tough for professionals treating "hard-core" patients who seem unable to benefit from treatment. The insurance law may give these victims another chance.

"A lot of our referrals come from a rehabilitation center," Ms Wright of Four Winds told the *Journal*. "These are the ones everyone says, 'forget it, they're not going to make it.' That's the kind I want. I work well with them."

"POOCH" tracks unimmunized children

The New York State Department of Health Immunization Program is offering physicians a system to keep track of preschool children who fail to keep immunization appointments.

A 1979 Health Department survey of about 600 two-year-old children disclosed that about a third of them were not on schedule for immunization. Most children in the general population who are not on schedule have at least begun their immunizations. The major problem, however, is that most of these children do not continue their immunization programs. In response to this problem, the New York State Department of Health Immunization Program is undertaking a variety of approaches to improve immunity levels among preschoolers, including teaching and counseling programs for new mothers, and telephone or personal contact with new mothers whose children are behind schedule.

The Department of Health and the School Health Committee of the Medical Society of the State of New York have developed a prototype patient recall system. This system, called POOCH (Provider Outreach for Ongoing Child Health), should prove useful in localities where no attempts are currently being made to recall the preschool children who receive their immunizations in public clinics. In New York State, however, private physicians administer between 70% and 80% of all immunizations given to infants and young children. Thus, an immunization recall system in broad use within the private sector would have the greatest impact on immunization levels in preschool children.

The POOCH immunization program provides some of the necessary materials, including immunization recall file cards, immunization record stickers or immunization record inserts, postcards, official New York State standard immunization record cards, and instructions.

The key element in the system is the immunization recall file card, one of which is prepared for each child. Because of the effectiveness of the present school immunization law in New York State, it is probably not necessary to include children over six in the system.

A file card is prepared for new patients during the initial visit, for patients who are already part of the physician's practice, and for any patient that a record review indicates should be part of the program. Immunization histories can be organized by applying immunization record stickers to the outside of each chart. When kept up to date, they provide a rapid, convenient method for determining a child's immune status. Alternatively, an immunization record insert can be incorporated into the patient's chart.

When a child arrives for an immunization, the immunization recall file card is attached to the record. The individual who administers the immunization enters that information in the appropriate location on or inside the chart. Prior to refiling the record, the chart is reviewed by the individual in charge of the POOCH system. This person enters the immunization data onto the immunization recall file card. The card is placed in the file box in alphabetical order behind the file divider indicating the month the child is due to return for the next immunization. At each succeeding visit, the child's card is pulled from the monthly file and attached to the chart, and the entire process is repeated.

At the end of each month, the person in charge of the POOCH system removes the remaining cards from the monthly file. These cards represent those children who failed to appear for their immunizations. Their families are called so new appointments can be scheduled. If a family is unreachable by telephone, a POOCH reminder post card is sent. When a new appointment is scheduled, the recall card is refiled behind the appropriate monthly file divider. File cards for children who could not be contacted are placed alphabetically behind a separate file divider labeled "Unscheduled" for future use, should they return. The previous month's file divider is moved to the rear of the file to accommodate cards of children who will be scheduled one year later.

When children complete their basic series (three doses of TOPV, four doses of DTP and one dose of MMR) at approximately 18 months, their cards should be filed alphabetically behind dividers indicating the year they will be returning for preschool physicals and TOPV and DTP boosters. Five annual file dividers should suffice. At the end of each year, the monthly procedure described previously is applied to the annual file. Parents should also maintain their own record using the New York State immunization record form.

Information on the POOCH system can be obtained by writing:

Immunization Program (POOCH)
New York State Department of Health
Room 649, Corning Tower
Empire State Plaza
Albany, NY 12237

Dennis O'Mara

The author, who served as assistant coordinator of the immunization program in the New York Department of Health, is Director of Immunization, Oklahoma State Department of Health.

FROM THE LIBRARY

THE TREATMENT OF CHRONIC ALCOHOLIC INEBRIETY

The treatment of poisoning with ptomains and drugs is well within the hands of the profession, but the treatment of alcohol poisoning and addiction still receives most of its attention from the mercenary exploiters of "cures." As the insane were until recently regarded as outside of the pale of medical attention, the unfortunate alcoholic is now. Still it is one of the commonest diseases, and except among the most enlightened the victim is regarded as being possessed of a vice just as the insane man was once regarded as possessed of a devil. If a man is found on the street suffering with opium poisoning he is conveyed to the hospital and receives scientific and humane treatment. If a man is found in the same place, suffering with alcoholic poisoning, he is taken in charge by the police, his ambulance is a patrol wagon, the treatment consists of a rap on the soles of the feet with a club and some supraorbital pressure, his hospital bed is the floor of a cell at the police station upon which he is tossed, and in the morning he appears before a judge and (not the police but the patient) is fined for committing a crime. Alcohol poisoning is a bad thing in the eye of the law.

It is much to be regretted that the treatment of this disease should be so largely in the hands of the quacks, who with their "institutes" and "cures" really do accomplish much in the treatment. It is surely a legitimate field for medical development; and, while some few regular physicians have given attention to the subject, it has by no means received the general attention which its importance merits. We have sufficient knowledge of the subject, surely more than the charlatans have, but it is possessed by too few practitioners. A good understanding of the nature and therapeutics of alcoholic inebriety should be possessed by every practitioner. Much can be done for these patients, many can be cured, and the honest doctor is the man for the work.

Mason,* who has made a careful study of the subject, attributes the good results which are attained by the charlatans to psychotherapy. The confidence of the patient is first won. Here comes in the value of the long list of clergymen and honorable citizens. Hope is aroused, a business transaction is consummated, money is paid, and an agreement to cure is given. No drug has any specific action against the disease, but the quack impresses his patient that the drugs are very expensive and very mysterious. It makes little difference what they are. A nauseating drug or something to dim the vision or create anorexia, such as atropine, serves but a temporary purpose. The drugs employed act along the lines of mental suggestion, and are in no sense specific.

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* Jour. A. M. A., Feb. 23, 1907.

—Editorial
NY State J Med 1907;7:501

COPE'S EARLY DIAGNOSIS OF THE ACUTE ABDOMEN

Sixteenth edition. Revised by William Silen, MD. 284 pp. New York, Oxford University Press, 1983. $12.95.

> *"The diagnostic problem of to-day*
> *Has greatly changed—the change has come to stay;*
> *We all have to confess, though with a sigh*
> *On complicated tests must rely*
> *And use too little hand and ear and eye."*
>
> ZACHARY COPE
> (*The Diagnosis of the Acute Abdomen in Rhyme*)

In the first edition of *Early Diagnosis of the Acute Abdomen*, published in 1921, Sir Zachary Cope stressed prompt clinical diagnosis of the cause of abdominal pain as the only way to avoid the tragedy of inordinate delay. Today, the diagnosis of acute abdominal pain remains a clinical one despite a surfeit of available laboratory procedures. It is in fact the misuse of technology that causes the dangerous delays today: a perceived need to confirm clinial impressions using an n-th generation scanner while awaiting clearer indications or hoping for spontaneous improvement.

This sixteenth edition of Cope's classic has been revised by Dr. William Silen, Johnson & Johnson Professor of Surgery at Harvard Medical School and Surgeon-in-Chief at Beth Israel Hospital in Boston. In his preface, Dr. Silen notes that "Some 19 years ago, I was asked by a publisher to write a treatise on the acute abdomen, but after serious consideration declined because it seemed impossible to improve on what Cope had already accomplished." Dr. Silen was wrong. The reader now has access to a unique combination of the viewpoints of two respected clinicians of vast experience in a text that has matured over 62 years into today's most concise, readable and authoritative text on the diagnosis of the acute abdomen.

Following four chapters on the basics [principles, history, examination, grouping of symptoms and signs], 18 subsequent chapters detail diagnosis and differential diagnosis from the common [appendicitis, peptic ulcers, cholecystitis] to the unusual [tropical diseases, diseases that simulate the acute abdomen]. The approach is always refreshingly logical. There are many useful tables and lists and a "Form for Acute Abdominal Cases," which will be useful to the neophyte. The emphasis is always on the common, although no conceivable etiology is overlooked. It is adequately illustrated with clear line drawings and includes 14 carefully selected radiographic plates that not only provide examples of such things as reduction of intussusception by barium enema, a classic case of gallstone ileus, and ultrasound examinations for aortic aneurysm and cholelithiasis, but also remind the reader of the few conditions for which diagnostic ultrasound or X-ray examination is indeed indicated. There is no bibliography, and in fact no need for one.

With surgeons as authors, one may be misled into considering *Early Diagnosis of the Acute Abdomen* a "surgical text". It is at least equally important that these principles be understood by those who examine the patient prior to surgical referral. This humble-appearing 284-page paperback should be read by every medical student, re-read by every house officer, and re-read periodically thereafter.

RICHARD M. STILLMAN, MD
SUNY, Downstate Medical Center
New York City 11203

A SHORT TEXTBOOK OF SURGERY

Fifth edition. By Selwyn Taylor, MCh and Leonard Cotton, MCh. 631 pp., illustrated. New York, Arco Publishing, Inc., 1983. $16.50.

This is the fifth edition of a popular short textbook of surgery authored by two distinguished British surgeons. Their goal has been to produce a compact and inexpensive review of surgery for family physicians, general internists, and medical students.

The book is clearly written, well organized, and comprehensive in the range of surgical subjects covered. It is illustrated by line drawings when these are necessary to clarify the text. Each chapter is followed by a brief and up-to-date bibliography that guides readers who seek more detailed information. Since it has been written by just two authors, there is greater consistency of style, less repetition and fewer gaps than in the texts with multiple authors. Inevitably, however, some sections are more current than others.

The text focuses primarily on clinical presentations and on surgical management. For the North American reader, the discussions of pathophysiology and of laboratory and radiographic diagnosis may seem relatively brief. Clearly, however, in a book that covers a range of topics similar to that of texts several times larger, the discussion of individual topics must necessarily be brief.

In general, this book is a remarkable achievement. It provides an overall introduction to the surgical field, including cardiothoracic, vascular, urologic, neurologic and pediatric subspecialties. All this is accomplished in an inexpensive, compact paperback volume of 600 pages. Discussion of some of the more common surgical conditions is, I believe, too brief to provide all of the information that a good medical student might be expected to acquire. Nonetheless, for a book of this size, the breadth of information is unique. It provides a valuable and easily read survey of surgery for students.

JOHN H. L. RANSON, MD
New York University
Medical Center
New York City 10016

SIMPLE SURGICAL EMERGENCIES

By Douglas Lindsey, MD. 262 pp., illustrated. New York, Arco Publishing, Inc. 1983. $12.

The author states on the cover of this book, "... if the solution to the emergent problem is straight-forward and negotiable without requiring great manual skill, it is considered a simple surgical emergency."

Dr Douglas Lindsey, associate professor of surgery, has presented a summary of his teachings to students at the University of Arizona. The book was written to help medical students in their clinical years prepare for their transition to a residency.

A wide variety of situations are discussed, from scalp lacerations and cranial burr holes to fractures, abdominal trauma and the insertion of a central venous line. The author discusses controversial issues, such as the value of topical antibiotics and the method of treatment of burns.

Some dogmatic statements may be questioned (e.g., "Never use absorbable sutures on a surface"); but, in general, Dr Lindsey offers good reasons for the diagnostic and therapeutic actions he recommends. The material is presented in an engaging way that is easy to follow and remember. Illustrative cases are included, and the line drawings are clear and helpful.

The wisdom of having a neophyte undertake some of the suggested procedures may be questioned (e.g. cranial burr holes), but the author indicates appropriately when it is time to "punt" (call for help from a senior or a specialist).

In a few instances the reader is left out on a limb. For example, in discussing insect bites, the author states, "the problem is anaphylaxis, and you know already how to treat that. Do so." There is no index to help the reader check on the way to handle anaphylaxis or pneumothorax.

Although there is a list of 135 pertinent references, including seven of the author's papers, they are arranged in alphabetical order at the end of the book. They might better have been included at the end of each chapter or group of chapters.

Simple Surgical Emergencies is recommended for those entering the phase of their medial training where surgical emergencies may be encountered for the first time, and for others who would like to review these situations. All will benefit from perusing the sensible guidelines that are presented clearly and in a manner that makes for "fun reading."

WILLIAM A. BARNES, MD
The New York Hospital
Cornell Medical Center
New York City 10021

CONCEPTS AND CONTROVERSIES IN CARDIOVASCULAR DISEASE

By Martin J. Kaplitt, MD, and Joseph B. Borman, FRCS 274 pp., illustrated. Norwalk, CT, Appleton-Century-Crofts, 1983. $27.50.

Hardcover books are often out of date before they are published. However, every now and then a monograph, even in hard cover, is sufficiently timely to be of practical value.

Martin J. Kaplitt of North Shore University Hospital, Manhasset, NY and Joseph B. Borman from Hadassah University Hospital, Jerusalem, are the editors of such a monograph. They have collected in their book a series of 26 papers taken from presentations by international cardiovascular groups at a meeting in Jerusalem on May 31–June 2, 1982. The subjects picked for publication from the meeting represent a number of controversial subjects in cardiovascular surgery and illustrate how they are solved by the various surgical teams. Although most of the groups originated in the United States (e.g., Brigham and Women's Hospital, Boston; Henry Ford Hospital, Detroit; Medical College of Pennsylvania and University of Pennsylvania, Philadelphia; Cleveland Clinic Foundation), Canada, England, Italy, Germany, the Netherlands and Israel are also represented.

The papers are divided into four major topics. The first, Surgery of Combined Coronary and Extracranial Vascular Disease, is introduced by a paper on Real Time Ultrasonography by Kaplitt et al, followed by papers from five centers describing their various approaches to the problem. These are short, interesting and informative. Statistical results are provided to support their methods.

The second topic is Concepts and Advances in Surgery for Valvular Heart Disease. After a State of the Art presentation by Ross of the National Heart Hospital in London, England, is the unduly long Value of Echocardiography from the Surgeon's Point of View, followed by six short papers on the virtues and problems associated with the use of the Starr-Edwards ball valve, the Medtronic-Hall tilting disc valve, the procine bioprosthesis, and xenograft value. The section ends with a paper by Borst et al from the Hannover Medical School, Hannover, Germany on Surgery for Active Infectious Endocarditis, an excellent exposition on the value of early surgery before the onset of circulatory failure.

The third topic, the Protection of the Ischemic Myocardia, starts with Myocardial Protection: Controversial Issues, by Borman and Shimon from Jerusalem, and is followed by Experimental Studies on Ischemic Contractive, and Recent Advances for Myocardial Protection. These papers concern themselves with the effects of varying degrees of ischemic contracture on systolic and diastolic recovery of the heart following reperfusion, and the ways to protect against this ischemic contracture.

The fourth topic presents Concepts in Surgery for the Ischemic Ventricle with discussions of the surgical treatment of life-threatening ventricular tachyarrhythmias, optimal pacing systems, the use of the intra-aortic balloon, left and right ventricular assists, and cardiac transplantation.

Concepts and Controversies in Cardiovascular Surgery serves the purpose intended by the authors, that of presenting different approaches to several cardiovascular problems, but does not provide the reader with the real give and take of true controversial discussions. The addition of commentaries about some of the papers by other authorities would have made the book more significant. The concepts are there, the controversies are only represented by many unanswered questions.

JOHN N. EDSON, MD
Long Island College Hospital
Brooklyn, NY 11201

Book Review Editor's Note: *Readers are invited to submit reviews of new books. Please contact the Book Review Editor for instructions.*

EMERGENCY MEDICINE: A QUICK REFERENCE FOR PRIMARY CARE

By John E. Hocutt, Jr, MD. 439 pp., illustrated. New York, Arco Publishing, Inc., 1983. $16.95.

In September 1979 the American Board of Emergency Medicine (ABEM) became the 23rd specialty board. The American Board of Medical Specialties recognized ABEM as a conjoint board of seven specialty boards (Family Practice, Internal Medicine, Obstetrics and Gynecology, Otolaryngology, Pediatrics, Psychiatry and Neurology, and Surgery) and three professional organizations (The American College of Emergency Physicians, The American Medical Association's Section of Emergency Medicine and the University Association for Emergency Medicine). Emergency Medicine is a multi-disciplinary specialty with responsibility for the care of patients with problems that may involve many branches of medicine. Formal training in approved emergency medicine residencies has expanded and is replacing the traditional single-specialty training programs as a source of emergency physicians. Full-time, career-oriented emergency physicians are replacing moonlighting specialists from other disciplines. At least four major textbooks of emergency medicine have been published since 1979, two of these consisting of large two-volume editions with more than 1700 pages.

Emergency Medicine: A Quick Reference for Primary Care was written by a board-certified family practitioner to "refresh one's memory in an organized and efficient manner" and to serve as a "source of information for the type of medicine every medical person sooner or later will face—emergency medicine". This book represents a conscientious and energetic effort to present treatment and care for all emergencies.

However, one slim volume cannot, nor should it attempt to, meet this broad goal. As it tries to serve as a quick reference book for many conditions, its coverage is too brief, sometimes being limited to a sentence or two. The volume does not provide sufficient information to enable a clinician to understand the problem, or to follow effectively the treatment guidelines. It may refresh one's memory, but not in enough depth to be of real value in a time of crisis, or to be of value to a clinician who only occasionally treats emergency patients.

The book consists of 40 chapters, ranging in length from a few pages to more than 35 pages. Each chapter is divided into three sections. One describes emergency room, office, and street care. These divisions work in some areas, while in others they are forced and useless.

The eight page chapter on Abdominal Pain illustrates the basic "quick reference" approach. The first three pages cover signs and symptoms, and the following five review 14 major causes of abdominal pain. The chapter stresses the need for surgical consultation, highlighting what the primary care physician should consider and do regarding the cause of abdominal pain.

A much more useful and comprehensive chapter is devoted to infectious diseases commonly seen in primary practice. The chapter covers general principles and stresses the importance of history and physical examinations in arriving at a working diagnosis. The chapter covers the principle infections and presents a logical approach to the diagnosis of these diseases. The author presents choices of antibiotics, alternate drugs, recommended dosages, and follow-up instructions.

The chapter of Cardiac Emergencies—Dysrhythmias, while nicely organized and illustrated with EKG tracings, suffers from being outdated. It was written without reference to verapamil. This drug is not included in any of the therapeutic modalities although it is the drug of choice for many dysrhythmias.

The last chapter, patient education, provides written handout material for distribution to patients, and complements well the book's efforts to enable primary care physicians to educate patients about their own medical problems.

Emergency medicine has grown rapidly into an approved specialty with its own concepts, principles, practitioners, and educational programs and texts. *Emergency Medicine—A Quick Reference For Primary Care* serves as a practical guide for primary care specialists who want to look up quickly something about a problem outside their specialty. It has limited benefit as a textbook or treatment manual for students and practitioners of emergency medicine.

ANTHONY C. MUSTALISH, MD
Lenox Hill Hospital
New York City 10021

MANAGEMENT OF WILDERNESS AND ENVIRONMENTAL EMERGENCIES

Edited by Paul S. Auerbach, MD and Edward C. Geehr, MD. 656 pp., illustrated. New York, Macmillan Publishing, 1983. $68.

Management of Wilderness and Environmental Emergencies is a successful presentation of the current diagnosis and treatment of problems in this aspect of emergency medicine. Written for all medical personnel, the textbook details, in 21 authoritative chapters, the spectrum of this growing and diverse field. The majority of contributors are national and international authorities in their fields as well as accomplished recreational and wilderness sportsmen. The editors are founding members of the Wilderness Medical Society.

The chapters cover such traditional topics as high altitude illness, hypothermia and heat, bites from arthropods, reptiles and mammals, aerospace and diving medicine, and a special chapter on drowning and near-drowning, lightning and inhalation injuries, and toxic plant reactions. There are also novel sections on mountain climbing, skiing, wilderness rescue, forest fires and disaster planning. Finally, there is an extensive appendix devoted to radiation accidents.

With few exceptions, the chapters are accurate and up-to-date. Each topic is considered from an historical, pathological, physiological, clinical, laboratory and therapeutic perspective. Case histories are often provided in order to clarify the salient clinical features of the section. References are accurate, recent, and useful to the generalist. The therapy described includes not only immediate emergency stabilization but also thorough aftercare. Recommendations are current and accurate.

Such difficult treatment areas as venomous snake bites are presented in an unbiased fashion. Each of the various traditional therapies is discussed and critiqued from a scientific perspective. A summary statement of the current treatment recommendations for snake bites is then made.

Of particular merit are the numerous summary tables that detail practical reference material that is usually not accessible to the busy clinician. Perhaps the only regret this reviewer has in critiquing the text is that there are no sections on such common outdoor hobbies as fishing, hunting and boating.

There is little extant work that compares to the breadth and depth of this textbook. In the years to come it should serve as an extremely useful and reliable reference source in managing environmental emergencies. The book is excellent, regardless of whether or not the reader is an outdoor enthusiast. With the remarkable resurgence of interest in wilderness activities, it is recommended that this book be easily accessible to physicians and other health professionals who handle these emergencies.

RICHARD BIRRER, MD
SUNY Downstate Medical Center
New York City 11203

CARDIOLOGY 1983

Edited by William C. Roberts, MD, 516 pp., illustrated. New York, NY, York Medical Books, 1983. $49.50.

Cardiology 1983 is a compilation of articles from the 1982 cardiologic literature, selected and briefly summarized by outstanding editors. It is the third in a series of annual volumes. Following a "journal club" approach, each of the principal editors reviewed articles from *Circulation*, *The American Journal of Cardiology*, or the *American Heart Journal*; other editors summarized articles from several journals. Dr. William C. Roberts, an experienced editor, then organized the summaries into a comprehensive text under eight major categories, such as Coronary Heart Disease, Acute Myocardial Infarction and its Consequences, Systemic Hypertension and Chronic Congestive Heart Failure. Ten percent of the volume is listed under "Miscellaneous Topics."

The individual summaries are well-written, more detailed than the abstracts that accompanied the original articles, and, generally, attempt to consider the reported facts in a broader context. In some instances, several articles dealing with a single subject are summarized together. However, there are no editorial summaries at the beginning or the end of each section, an addition that would have been useful to the general reader. The format makes reading difficult. Most papers are reviewed in single and often long paragraphs. Article summaries are not separated by sub-titles, and the illustrations are reproduced with dark backgrounds.

A review of this sort is of use to busy practitioners who wish to rely on experts to cull the literature and summarize what they consider to be important articles. However, most readers would be better served by well-written reviews of annual progress in broad areas rather than a compilation of summaries. For the cardiologist or internist who keeps up with the major journals, a compilation of this sort is useful to jog the memory about articles previously read and forgotten or to call attention to overlooked topics. It is a useful exercise to look through the table of contents in *Cardiology, 1983*, and pick out papers with which one is unfamiliar. This process is perhaps more efficient than sitting down for a few hours in a medical library, reviewing the indices of the major journals, and then reading the complete papers.

Cardiology, 1983, is certainly of greater reliability and usefulness to the generalist and to the cardiologist than the many reviews in throwaway journals with which we are deluged daily. It is not an easy review to read for general information, but the quality of the individual summaries is high and the overall selection process by the educator-editors is superb.

ARTHUR C. FOX, MD
New York University Medical Center
New York City 10016

BOOKS RECEIVED

PSYCHIATRY

The Loss of Loved Ones: The effects of a death in the family on personality development. Edited by David M. Moriarty, MD. 292 pp., illustrated. St. Louis, MO, Warren H. Green, 1983. $27.50 (hardcover).

Healing in Psychotherapy: The process of holistic change. By Diane Shainberg. 126 pp. New York, Gordon and Breach Science Publishers, 1983. $37.50 (hardcover).

GERIATRICS

Handbook of Geriatric Drug Therapy for Health Care Professionals. By Edward D. Sumner, PhD. 208 pp. Philadelphia, PA, Lea & Febiger, 1983. $14.00 (softcover).

Rehabilitation in the Aging. Edited by T. Franklin Williams, MD. 389 pp., illustrated. New York, Raven Press, 1983. $39.50 (hardcover).

ALLERGY

Mould Allergy. Edited by Yousef Al-Doory PhD and Joanne F. Domson, MD. 287 pp., illustrated. Philadelphia, PA, Lea & Febiger, 1984. $28.50 (hardcover).

LABORATORY MEDICINE

Saunders Dictionary and Encyclopedia of Laboratory Medicine and Technology. By James L. Bennington, MD. 1700 pp., illustrated. Philadelphia, PA, W. B. Saunders Company, 1984. $45.00 (hardcover).

IMMUNOLOGY

Fundamentals of Immunology. Second edition. Edited by Quentin Myrvik, PhD and Russell S. Weiser, PhD. 510 pp., illustrated. Philadelphia, PA., Lea & Febiger, 1983. $24.50 (hardcover).

CARDIOLOGY

Congenital Heart Disease After Surgery: Benefits, residua, sequelae. Edited by Mary Allen Engle, MD and Joseph K. Perloff, MD. 420 pp., illustrated. New York, Yorke Medical Books, 1983. $40.00 (hardcover).

PARASITOLOGY

Clinical Parasitology. Ninth edition. By Paul Chester Beaver, PhD, Rodney Clifton Jung, MD, and Eddie Wayne Cupp, PhD. 825 pp., illustrated. Philadelphia, PA, Lea & Febiger, 1984. $51.50 (hardcover).

ONCOLOGY

An International Survey of Distributions of Histologic Types of Tumours of the Testis and Ovary. Edited by Helge Stalsberg. 350 pp., illustrated. Bern, Switzerland, Hans Huber, 1983. $24.00 (softcover).

Cancer in Brazil: Histopathological data—1976-80. Edited by Rodolfo Brumini. 433 pp., illustrated. Rio de Janeiro, Brazil, Ministerio da Saude, 1983. (hardcover).

NEUROLOGY

The Assessment of Aphasia and Related Disorders. By Harold Goodglass, PhD and Edith Kaplan, PhD. 102 pp., illustrated. Philadelphia, PA, Lea & Febiger, 1983. $27.00 (hardcover).

Alzheimer's Disease: The Standard Reference. Edited by Barry Reisberg, MD. 475 pages. New York, The Free Press, 1983. $45.00 (hardcover).

INTERNAL MEDICINE

Preventing Reactive Hypoglycemia: The great medical dilemma. By Fred D. Hofeldt, MD. 135 pp., St. Louis, MO, Warren H. Green. 1982. $18.50 (hardcover).

In addition to these listings, the Journal will publish obituaries written by physician readers. Inquiries should first be made to the Editor.

Jerome Karl Asch, MD, Freeport. Died September 18, 1983; age 71. He graduated in 1934 from Boston University School of Medicine. Dr Asch was a member of the Nassau County Medical Society and the Medical Society of the State of New York.

John William Banzer, Jr, MD, Rockville Centre. Died September 19, 1983; age 71. Dr Banzer graduated in 1943 from Georgetown University School of Medicine and was a member of both the Nassau County Medical Society and the Medical Society of the State of New York.

Chaim Ben-Dashan, MD, Corning. Died August 13, 1983; age 56. Dr Ben-Dashan graduated from the University of Cape Town Faculty of Medicine, Cape Town in 1950 and was a member of the Steuben County Medical Society and the Medical Society of the State of New York.

Howard Thomas Blair, MD, Brooklyn. Died September 27, 1983; age 89. He graduated from New York Medical College, Flower and Fifth Avenue Hospitals, New York in 1916. Dr Blair was a Fellow of the American College of Surgeons, and a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Max Cheplove, MD, Buffalo. Died September 6, 1983; age 81. Dr Cheplove graduated from the University of Buffalo School of Medicine in 1926. He was a Fellow of the American Academy of Family Practice and his memberships included the Pan American Medical Association, the Medical Society of the County of Erie, and the Medical Society of the State of New York.

Stanley L. Edmunds, MD, Glens Falls. Died August 15, 1983; age 76. Dr Edmunds was a 1932 graduate of the State University of New York Upstate Medical Center-Syracuse. He was a Diplomate of the American Board of Otolaryngology, a Fellow of the American College of Surgeons and his memberships included the Academy of Medicine, the American Academy of Otolaryngology, the American Academy of Facial Plastic and Reconstructive Surgery, the Medical Society of the County of Warren, and the Medical Society of the State of New York.

James Joseph Farley, MD, New York. Died September 7, 1983; age 83. He attended the New York University College of Medicine and graduated in 1923. Dr Farley was a member of the Academy of Medicine, the American Academy of Family Practice, New York County Medical Society, and the Medical Society of the State of New York.

Neil Fitch Forbes, MD, Flushing. Died July 5, 1983; age 84. In 1924 he graduated from Columbia University College of Physicians and Surgeons and was a member of the Queens County Medical Society and the Medical Society of the State of New York.

Jack Froman, MD, New York. Died September 9, 1983; age 75. He graduated from the Universitat Bern Medizinische Fakultat in 1937. Dr Froman was a member of New York County Medical Society and the Medical Society of the State of New York.

Clarence F. Heyden, MD, Buffalo. Died June 19, 1983; age 78. He was graduated from the University of Buffalo School of Medicine in 1930 and was a member of the Medical Society of the County of Erie and the Medical Society of the State of New York.

Morris Kaplan, MD, New York. Died September 6, 1983; age 85. Dr Kaplan was a 1921 graduate of Columbia University College of Physicians and Surgeons. He was a Diplomate of the American Board of Radiology, a Fellow of the American College of Chest Physicians, a Fellow of the American College of Radiology, a Fellow of the American College of Gastroenterology, a member of the Radiological Society of North America, Inc, the New York Roentgen Society, the New York County Medical Society, and the Medical Society of the State of New York.

Julius Pincus, MD, Cedarhurst. Died August 22, 1983; age 88. He attended the State University of New York Downstate Medical Center (Long Island College Hospital) and graduated in 1916. Dr Pincus was a Diplomate of the American Board of Pathology, a Fellow of the American College of Pathologists, and a member of the New York Pathological Society, the New York State Society of Pathologists, the American Society of Clinical Pathologists, the New York County Medical Society, and the Medical Society of the State of New York.

James Craig Potter, MD, Rochester. Died August 22, 1983; age 85. He graduated from Johns Hopkins University School of Medicine in 1921. Dr Potter was a Diplomate of the American Board of Obstetrics and Gynecology, a Fellow of the American College of Surgeons, a Fellow of the American College of Obstetricians and Gynecologists, a member of the Academy of Medicine, the Medical Society of the County of Monroe, and the Medical Society of the State of New York.

Rieva Rosh, MD, New York. Died September 19, 1983; age 86. Dr Rosh graduated from the Kharkov Medical Institute, Kharkov, Ukranian S.S.R. in 1922. She was a Diplomate of the American Board of Radiology, a Fellow of the American College of Radiology and a member of the Academy of Medicine, the New York Roentgen Society, the Radiological Society of North America, the American Radium Society, New York County Medical Society and the

Medical Society of the State of New York.

A. Alfred Solomon, MD, Far Rockaway. Died May 9, 1983; age 78. He attended New York University College of Medicine, New York and graduated in 1930. Dr Solomon was a Diplomate of the American Board of Urology, a Fellow of the American College of Surgeons, a member of the Academy of Medicine, the American Urological Association, New York County Medical Society, and the Medical Society of the State of New York.

Leon A. Stetson, MD, Rochester. Died August 28, 1983; age 87. Dr Stetson graduated from the Hahnemann Medical College and Hospital of Philadelphia in 1923 and his memberships included the Academy of Medicine, the American Occupational Medical Association, the Medical Society of the County of Monroe and the Medical Society of the State of New York.

William I. Walsh, MD, Troy. Died August 13, 1983; age 92. Dr Walsh graduated in 1914 from Albany Medical College of Union University. He was a member of both the Medical Society of the County of Rensselaer and the Medical Society of the State of New York.

Daniel W. Wilbur III, MD, Huntington. Died September 17, 1983; age 68. Dr Wilbur was graduated from Columbia University College of Physicians and Surgeons in 1940. He was a Diplomate of the American Board of Obstetrics and Gynecology, a Fellow of the American College of Surgeons, a Fellow of the American College of Obstetricians and Gynecologists, a member of the American Fertility Society, the Suffolk County Medical Society, and the Medical Society of the State of New York.

Herbert F. Wilshusen, MD, Fryeburg, Maine. Died September 23, 1983; age 87. Dr Wilshusen was graduated from the Columbia University College of Physicians and Surgeons in 1921. He was a member of both the Medical Society of the County of Westchester and the Medical Society of the State of New York.

Glenn Aldrich Wood, MD, Largo, Florida. Died August 23, 1983; age 93. Dr Wood graduated from the State University of New York Upstate Medical Center-Syracuse in 1918 and was a member of the Onondaga County Medical Society and the Medical Society of the State of New York.

Guidelines for authors

ORIGINALITY

The *New York State Journal of Medicine* welcomes research papers and original essays on the practice of medicine, medical education, public health, the history of medicine, medicolegal matters, legislation, ethics, the mass media and socioeconomic issues in health care.

Manuscripts should be prepared according to the "Uniform requirements for manuscipts submitted to biomedical journals" (*NY State J Med* 1983; 83:1089–1094. The requirements were established by the International Committee of Medical Journal Editors, of which the *Journal* is a participating member. These Guidelines are intended to highlight aspects of the *Journal*'s particular style of publication.

A manuscript will be considered for publication if it is original, has not been published previously in whole or in part in either a medical journal or a lay publication, and is not simultaneously under consideration elsewhere. A copy of any possibly duplicative material, such as a reference "in press," should be submitted along with the manuscript.

PREPARATION

An original typewritten or "word-processed" manuscript and two photocopies (to facilitate outside review) are required. If the manuscript is not accepted for publication, the original and one copy will be returned. All figures must be submitted in triplicate. The manuscript should be double-spaced throughout, including references, tables, legends, quotations, and acknowledgments. A separate title page should include the full title of the paper in upper and lower case type, the names of the authors exactly as they should appear in print (including their highest academic degree), an abbreviated title of no greater than 40 spaces for use as a running foot, and the names of all providers of funding for research on which the paper is based. Information on the amount and allocation of funding is optional.

A corresponding author should be designated in the covering letter. Authors should list their title and affiliation at the time they did the work, and, if different, their present affiliation. The addresses and telephone numbers of all authors should be supplied for editorial purposes. All authors of a manuscript are responsible for having read and approved it for submission.

CATEGORIES

Research Papers should be limited to 2,500 words and should include the following sections: Introduction, Methods, Results, Discussion, and References. Multiple subheadings and numbered lists are discouraged. An abstract limited to 150 words should state the reasons for the study, the main findings, and their implications. Statistical evaluations should be described in the Methods section, and the name and affiliation of the statistician should be included in the acknowledgments if this individual is not listed as a coauthor. Reports of experiments involving human subjects must include a description in the Methods section of the informed consent obtained and a statement that the procedures followed were approved by an institutional research review committee. Anonymity of patients must be preserved. Reports of experiments on animals must note which guidelines were followed for the care and use of laboratory animals.

Case Reports should be limited to 1,250 words. Review Articles should not exceed 3,000 words. Commentaries should be between 750 and 1,000 words. Other kinds of original essays should not exceed 2,000 words. A letter of inquiry should be sent to the editor prior to submitting a Review Article or Commentary.

For Research Papers only, scientific measurements should be given in conventional units, with Systéme Internationale (SI) units in parentheses. Abbreviations and acronyms should be kept to a minimum, and jargon should be avoided. Generic names of drugs should be used instead of brand names.

FIGURES

The submission of color illustrations or slides is discouraged. Only black and white glossy photographic prints or "camera-ready" artwork will be accepted. The *Journal* is unable to provide art services such as the addition of arrows to photographs. A signed consent for publication must accompany photographs in which the patient is identifiable. Illustrations from other publications generally will not be considered. Legends for illustrations should be typed on a separate sheet, and for photomicrographs should include magnification and stain. Each illustration should be lightly marked on the back in pencil with the name of the first author, the number as cited in the text, and an arrow indicating the top. Each set of illustrations should be submitted unmounted in a separate envelope.

Tables should be simple, self-explanatory, and few in number. Each table should be typed double-spaced on a separate sheet.

REFERENCES

References should be limited to the most pertinent. The recommended maximum number of references is 25 for Research Papers and most other original contributions (except lengthier Review Articles), 12 for Commentaries and Case Reports, and six for letters to the editor.

Authors are responsible for the accurate citation of references. Citation of secondary sources is discouraged except where the original reference is unobtainable. Authors may not cite references they have not read, and the use of abstracts as references should be avoided.

References should be indicated in the text by superscript numbers following the name of the author (eg, Smith^2 reported two cases).

The list of references at the end of the article should be typed double-spaced and references should be numbered in the order in which they appear on the text. When there are six or fewer authors, all should be listed; where there are seven or more, the first three should be listed, followed by *et al.* Names of journals should be abbreviated according to *Index Medicus* and underlined.

Sample references:

1. Kepes ER, Thomas P, Vemulapalli K: Methadone and intravenous morphine requirements. *NY State J Med* 1983; 83:925–927.
2. McGuigan JE. Peptic ulcer. In: Petersdorf RG, Adams RD, Braunwald E, Isselbacher KJ, Martin JB, Wilson JD, eds. ***Harrison's Principles of Internal Medicine.*** New York, McGraw-Hill, 1983, pp 1697–1712.

REVIEW

All manuscripts are reviewed by the editors, and most manuscripts are sent to outside referees. Decisions concerning acceptance, revision, or rejection of a manuscript are usually made within three to six weeks. Every effort will be made to assure prompt publication of an accepted manuscript. A galley proof will be sent to the author for approval prior to publication.

Address correspondence to Alan Blum, MD, Editor, *New York State Journal of Medicine*, P.O. Box 5404, 420 Lakeville Road, Lake Success, NY 11042.

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Albany, New York 12207
(518) 472-4427/4463

Western New York State
Navy Medical Programs
Federal Building
111 West Huron Street
Buffalo, New York 14202
1-800-822-8838

(*continued from page 10A*)

Office of Disability Determinations, 110 William St, New York, NY 10038. Tel: (212) 587-3770.

Mar 15–17. **Surgical Course in Lens Implantation.** Info: Ruth Green, Administrator, Ophthalmologic Foundation of America, 823 United Nations Plaza, New York, NY 10017. Tel: (212) 986-4848.

Mar 15–17. **Human Values and Cancer.** Info: Fourth National Conference on Human Values & Cancer, American Cancer Society, 777 Third Ave, New York NY 10017. Tel: (212) 371-2900.

Mar 19–23. **Seminar in Advanced Rheumatology.** 29 Cat 1 credits. *Mar 26–30.* **Anesthesiology: Comprehensive Review III.** 40 Cat 1 credits. Info: Mary Ann Giammarino, NYU Post Graduate Medical School, 550 First Ave, New York, NY 10016. Tel: (212) 340-5295 (24 hr service).

Mar 20. **Metropolitan AIDS Project.** 1 Cat 1 credit. Info: Mrs V Matthes, Admin Secy, Society for Liaison Psychiatry, 542 Baldwin Ave, Baldwin, NY 11510. Tel: (516) 379-1787.

Mar 30. **Brachytherapy Oncology Update.** 7 Cat 1 credits. Info: Ms Dina Mastoras, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10021.

BRONX

Mar 22. **Organ Transplantation.** 6 Cat 1 credits. Info: Grace Urrows, Public Interest Dept, Montifiore Medical Center, 111 E 210 St, Bronx, NY 10467. Tel: (212) 920-4011.

BROOKLYN

Mar 7. **Cobalamin Deficiency.** *Mar 14.* **Treatment of Hodgkins Disease.** *Mar 21.* **Cytogenetics and Hematologic Disorders.** *Mar 28.* **Surface Marker Analysis in Leukemias.** Info: Division of Hematology/Oncology, Interfaith Medical Center, 555 Prospect Place, Brooklyn, NY 11238. Tel: (212) 240-1211 or 1212.

Mar 19. **Cardiopulmonary Resuscitation.** *Mar 20.* **Anesthesia for Cerebrovascular Surgery.** 1 Cat 1 credit per lecture. Info: Abraham I Raskob, MD, Dept of Anesthesiology, SUNY Downstate Medical Center, 450 Clarkson Ave, Brooklyn NY 11203. Tel: (212) 270-1233.

QUEENS

Mar 1. **The Chronically Enlarged Node.** *Mar 8.* **Sleep Apnea.** 1 Cat 1 credit per lecture. Info: Clo Vezza, Booth Memorial Medical Center, 56-45 Main St, Flushing, NY 11355. Tel: (212) 670-1419.

Mar 6. **The Patient with Chest Pain: Pathophysiology, Differential Diagnosis and Treatment.** *Mar 13.* **Nosocomial Pneumonias and Pneumonias in the Immunosuppressed Host.** *Mar 20.* **Lymphomas**

(*continued on page 18A*)

1984 ANNUAL CME ASSEMBLY

PRESENTED BY THE

Medical Society of the State of New York

JUNE 29 - JULY 1

Sheraton Centre

Seventh Ave. & 52nd St.

New York City

☐

HIGHLIGHTS . . .

General Session: Medicine in this Age of Violence • 26 Sessions • Panel Discussions • Meet the Professor • Scientific & Technical Exhibits • Medical Society Reception

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Single Room	$76	$84	$98
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Medical Society
of the
State of New York
June 29–July 1, 1984

Reservations must be received by hotel no later than June 8.
IF RATE REQUESTED IS NOT AVAILABLE, NEXT AVAILABLE RATE WILL APPLY, RESERVATIONS RECEIVED AFTER SPECIFIED DATE WILL BE ACCOMMODATED ON A RATE AND SPACE AVAILABILITY BASIS ONLY.

Checkout time is 1:00 p.m. Normal Check in time is after 3:00 p.m.

Reservations are held until 6:00 p.m. unless guaranteed by a one nights deposit or guaranteed with one of the following credit cards: Diners Club, Carte Blanche, American Express.

Credit Card # ____________________ Exp. date ____________ Type ____________

General Information

Our CME Sessions are open to all physicians and the allied professions. The three full days of meetings will provide the individual physician with a possible 25 credits out of a total of 100, Category 1, CME credit hours being offered. Over 120 outstanding speakers, including a number from out-of-state, will present papers at 26 sessions. A highlight of the Assembly will be a general session on "Medicine in this Age of Violence," to be presented on Saturday, June 30th. Some areas to be discussed will be violence on the highway, in sports, in institutions, in war, sexual abuse of children, and drug abuse in adolescents.

Returning by popular request, "Meet the Professor" sessions will take place on Friday, June 29th. There will be six, 1½ hour sessions scheduled throughout the day.

Our program covers a wide range of medical specialties and focuses on helping the practicing physician meet the daily needs of patient care. You can be assured of an interesting program.

In addition, there will be Scientific and Technical Exhibits on display to update the physician on developments in both areas. Complimentary coffee breaks will be scheduled in the mornings and afternoons to allow time for physicians to visit the exhibits.

A reception for physicians and exhibitors, compliments of the Medical Society of the State of New York, will be held on Friday, June 29, from 6-7 pm. As the Assembly date closely precedes the 4th of July, we suggest that you bring your family to enjoy a pre-holiday weekend in New York City before continuing to your destination. The Sheraton Centre provides valet parking for your convenience.

Among the many new attractions in New York City are the downtown *South Street Seaport Museum,* a restoration of the early 19th century seaport that was engaged in trade and commerce. Here we find historic sailing ships at Pier 16, a multi-screen movie presentation of the early trading days, the Fulton Market with its restaurants, cafes, food shops, plus many specialty shops in the area. Uptown on Fifth Ave., the new *Trump Tower* presents a breathtaking, multilevel atrium lobby lined in pink marble, waterfalls and tropical plants. Escalators take you to international shops on each level. Visit the legendary WWII Aircraft Carrier *Intrepid, Sea-Air Space Museum* at Pier 86, a must experience for the entire family. Bring your family and join your colleagues for a weekend of stimulating CME sessions.

HOTEL RESERVATIONS

Physicians must make their own hotel reservation no later than June 8, 1984. If making reservations by telephone, please identify the Medical Society meeting for the special rate to apply.

REGISTRATION

Registration will take place in the Exhibition Centre, located on the lower level of the hotel. For those who registered in advance, your ID Badge will be held at the Medical Society Registration Desk. All new registrants must present identification at the registration desk.

REGISTRATION HOURS

Friday & Saturday —
8:30 a.m.-5:00 p.m.
Sunday — 8:30 a.m.-4:30 p.m.

MEETING HOURS

Friday — Meet the Professor,
8:30 a.m.-5:30 p.m.
All other meetings,
9:00 a.m.-5:00 p.m.
Saturday & Sunday —
9:00 a.m.-5:00 p.m.

1984 ANNUAL CME ASSEMBLY

Medical Society of the State of New York
Sheraton Centre, New York City

FRIDAY, JUNE 29

Morning	Cardiovascular Diseases, Royal Ballroom A
	Cancer Update, Versailles Terrace
	Pediatrics/School Health, Royal Ballroom B (all day)
	Meet the Professor, Consulate Suite Regency Foyer
Afternoon	Pediatrics/School Health, Royal Ballroom B
	Neurosurgery, Versailles Terrace
	Medical Legal & Workers' Compensation/Occupational Medicine, Royal Ballroom A
	Neurology, Regency Ballroom
	Meet the Professor, Consulate Suite Regency Foyer

SATURDAY, JUNE 30

Morning	Chest Diseases, Regency Ballroom
	Internal Medicine, Georgian Ballroom A (all day)
	Ophthalmology, Royal Ballroom A (all day)
	General Session "Violence", Georgian Ballroom B (all day)
	Obstetrics/Gynecology, Versailles Terrace
	Hand Surgery, Royal Ballroom B (all day)
Afternoon	Internal Medicine, Georgian Ballroom A
	Ophthalmology, Royal Ballroom A
	General Session "Violence", Georgian Ballroom B
	Dermatology/Otolaryngology, Versailles Terrace
	Pathology/Gastroenterology, Regency Ballroom
	Hand Surgery, Royal Ballroom B

SUNDAY, JULY 1

Morning	Allergy & Immunology, Georgian Ballroom A
	Family Practice/Preventive Medicine/Psychiatry, Royal Ballroom B (all day)
	Orthopedic Surgery/General Surgery/Plastic Surgery/Physical Medicine & Rehabilitation/Radiology/Anesthesiology, Georgian Ballroom B (all day)
	Urology/Emergency Medicine, Royal Ballroom A
	Women's Medical Society of New York State, Versailles Terrace
Afternoon	Family Practice/Preventive Medicine/Psychiatry, Royal Ballroom B
	Orthopedic Surgery/General Surgery/Plastic Surgery/Physical Medicine & Rehabilitation/Radiology/Anesthesiology, Georgian Ballroom B
	Alcoholism, Royal Ballroom A

□

CME CREDITS: Each program will be eligible for CME Category 1 credits on an hour-for-hour basis.

□

Technical & Scientific Exhibits

Advance Registration Form

Complete and return this form to the Medical Society address as indicated below.

1984 Annual CME Assembly, June 29–July 1

SHERATON CENTRE, NEW YORK CITY

PLEASE PRINT

Name ____
LAST *FIRST*

Address ____

City/State/Zip ____

GENERAL REGISTRATION FEE

Please check category

☐ MSSNY Active Member	$25.00
☐ MSSNY Life Member	$10.00
☐ Non-member physician	$50.00
☐ Allied Profession	$10.00

Medical Specialty ____________________

Please check category

- ☐ Nurse
- ☐ Physician Assistant
- ☐ Dentist
- ☐ Lab Technician
- ☐ PT/OT
- ☐ Medical Writer
- ☐ Other (Specify) ____________________

NO FEE

- ☐ Speaker
- ☐ Medical Student
- ☐ Medical Assistant
- ☐ Resident/Intern
- ☐ Spouse/Family
- ☐ News Media

MEET THE PROFESSOR

Friday, June 29th only. Fee: $25.00 per session. Please indicate session(s) attending. The six, 1½ hour sessions are limited to 30 persons each.

- ☐ 8:30 a.m. – Stephen Scheidt, M.D.
- ☐ 10:00 a.m. – Richard Gorlin, M.D.
- ☐ 11:30 a.m. – Howard Spiro, M.D.
- ☐ 1:00 p.m. – Eli Friedman, M.D.
- ☐ 2:30 p.m. – Philip Felig, M.D.
- ☐ 4:00 p.m. – Harold Neu, M.D.

(See this issue for subjects to be presented by each Professor)

REMITTANCE

Registration Fee $ ______________
Meet the Professor session(s) $ ______________
TOTAL $ ______________

Please make check payable to:
Medical Society of the State of New York, and return this form with remittance to: Division of Meeting Services, MSSNY, 420 Lakeville Rd., P.O. Box 5404, Lakeville, N.Y. 11042.

Important: Your ID Badge will be held at the MSSNY Registration Desk located in the Exhibition Centre, lower level, Sheraton Centre.

Meet the Professor — JUNE 29th

at the Medical Society of the State of New York's Annual CME Assembly, June 29-July 1, Sheraton Centre, New York City. Three sessions, 1½ hours each, will be offered on Friday morning, and three on Friday afternoon. Sessions are limited to 30 attendees each, and there is a $25.00 fee per session. Please see the registration form on the facing page.

Felig

Friedman

Philip Felig, M.D.

Professor of Medicine & Chief of Endocrinology, Yale University School of Medicine, New Haven, Connecticut. This session will deal with newer intensive approaches to the management of diabetes, including self-monitoring of blood glucose, multiple insulin injections and insulin pump therapy.

Eli A. Friedman, M.D.

Professor of Medicine, Chief, Division of Renal Disease, SUNY Downstate Medical Center, Brooklyn, N.Y. Uremia therapy is one of the great successes of this century. There are currently more than 250,000 patients sustained by maintenance hemodialysis, peritoneal dialysis, and renal transplantation. The importance of identification and appropriate preparation of candidates for these therapies is self evident. The major causes of renal failure, its conservative management, and the advantages and problems of each therapeutic option will be considered.

Richard Gorlin, M.D.

Professor & Chairman of Medicine, Mount Sinai Hospital, New York City.

Harold Neu, M.D.

Professor of Medicine & Pharmacology, & Chief, Division of Infectious Diseases, Columbia University College of Physicians & Surgeons, New York City. This lecture will attempt to place all of the cephalosporin antibiotics in perspective so that the practicing physician will know when to use these drugs.

Stephen Scheidt, M.D.

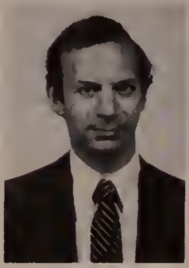
Professor of Clinical Medicine, New York Hospital-Cornell Medical Center, New York City. To update the practicing physician on current knowledge concerning calcium blockers, including new data on arrhythmias, vasospastic angina, chronic stable angina, IHSS, hypertension, and other current or potential indications for their use.

Howard M. Spiro, M.D.

Professor of Medicine, Yale University School of Medicine, New Haven, Connecticut. Update the practicing physician on clinical and technological advances in gastroenterology while keeping the patient's problem as a focus.

Gorlin

Neu


Scheidt

Spiro

Gene Luttenberg

Doctor . .

Do you, or a physician you know, have a problem with alcoholism, drug abuse, emotional illness or other difficulties which interfere with the ability to practice medicine?

If so, please contact the Medical Society of the State of New York's Physicians' Committee, whose function is to assist impaired physicians, at the following confidential number: 516-488-7777.

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(*continued from page 12A*)

Update. *Mar 27.* **Dermatology for the Non-Dermatologist.** 1½ Cat 1 credits per lecture. Info: Luisa T. Gonzalez, Coordinator, CME, Flushing Hospital and Medical Center, 4500 Parsons Boulevard, Flushing, NY 11355-9980. Tel: (212) 670-5741.

NASSAU

Mar 2. **Fetal Uptake and Distribution of Analgesics and Anesthetics.** *Mar 9.* **Clinical Pathology Conference.** *Mar 16.* **Apnea and Sudden Infant Death Syndrome.** *Mar 30.* **Development of the Hypothalamo-Pituitary System and its Disorders in the Newborn.** Info: Nergesh Tejani, MD, OB-Gyn, Nassau County Medical Center, 2201 Hempstead Turnpike, East Meadow, NY 11554. (516) 542-2257.

SUFFOLK

Mar 1. **Trauma Management in the 80's.** 6 Cat 1 credits. *Mar 14–18.* **Family Medicine Update.** 39 Cat 1 credits. *Mar 31.* **The Low Back Problem: New Methods of Diagnosis and Treatment.** 4 Cat 1 credits. Info: Tamarath K Yolles, MD, Association Dean for Continuing Medical Education, School of Medicine (HSC), SUNY at Stony Brook, Stony Brook, NY 11794. Tel: (516) 444-2094.

Mar 6. **Neonatology in the Level II Hospital.** *Mar 13.* **The Immunology of Asthma.** Info: Arthur Schwager, MD, Chairman, Pediatric CME, Huntington Hospital, 270 Park Ave, Huntington, NY 11743. Tel: (516) 427-0530.

WESTCHESTER

Mar 14. **Depression and Paranoia in the Elderly.** White Plains. Info: Sally Jo Tourjee, Harlem Valley Psychiatric Center, Wingdale, NY 12594. Tel: (914) 832-6611.

ST. LAWRENCE

Mar 15. **Intracranial Pressures, Approach and Treatments.** Info: Sebastian A Mazzotta, MD, Program Chairman, Medical Society of the County of St Lawrence, Canton-Potsdam Hospital, 50 Leroy St, Potsdam, NY 13676. Tel: (315) 265-3300, x-4202.

(*continued on page 25A*)

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Start with 80 mg once daily...

Dosage may be increased to 120 mg or 160 mg once daily as needed to achieve additional control. When converting patients from other beta blockers, including INDERAL tablets, start with the nearest milligram equivalent of INDERAL LA once daily and evaluate clinical results to determine if dosage adjustment is necessary. For arrhythmias, use conventional INDERAL (propranolol HCl) tablets.

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Please see next page for brief summary of prescribing information.

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for HYPERTENSION, ANGINA
and prevention of MIGRAINE.

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INDERAL® LA

(PROPRANOLOL HCl) LONG ACTING CAPSULES

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION SEE PACKAGE CIRCULAR.)*
INDERAL® LA BRAND OF propranolol hydrochloride
(Long Acting Capsules)

DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.

CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity.

In dosages greater than required for beta-blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain.

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma; 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL

WARNINGS. CARDIAC FAILURE. Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

> IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)— PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. General: Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug

Pregnancy: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Nursing Mothers: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy

Cardiovascular. bradycardia; congestive heart failure; intensification of AV block, hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System. lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia, visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized.* The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily The dosage may be increased gradually to achieve optimum migraine prophylaxis If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily

PEDIATRIC DOSAGE — At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

*The appearance of INDERAL LA capsules is a registered trademark of Ayerst Laboratories.

8688/883

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(*continued from page 18A*)

AROUND THE NATION

CALIFORNIA

Mar 1–3. **Immunology and the Clinical Practice of Allergy.** San Diego. Info: Office of Continuing Medical Education. UCSD School of Medicine, M-017, La Jolla, CA 92093. Tel: (619) 452-3940.

Mar 12–16. **International Academy of Pathology Meeting—US-Canadian Division. San Francisco.** Info: US-Canadian Division of the International Academy of Pathology, 1003 Chafee Ave, Augusta, GA 30904. Tel: (404) 724-2973.

Mar 16–18. **Office Emergencies in Primary Care.** 20 Cat 1 credits. San Diego. Info: Jacqueline Shiller, M Ed, CMEA, PO Box 84296, San Diego, CA 92138. Tel: (619) 223-2997.

Apr 11–14. **Current Concepts in Surgical Pathology.** 3 Cat 1 credits per workshop (21 credits total). Stanford. Info: Leslie Culligan, Laboratory of Surgical Pathology, Stanford University Medical Center, Room P-2020, Stanford, CA 94305. (415) 497-7211.

COLORADO

Mar 5–9. **Infectious Diseases.** 23¾ Cat 1 credits. Snowmass. Info: J. Remington, Research Institute—Palo Alto Medical Foundation, 860 Bryant, Palo Alto, CA 94301. Tel: (415) 321-4121.

Apr 6–8. **Advanced Cardiovascular Diagnostic and Therapeutic Methods.** 18 Cat 1 credits. Info: Mary A Schroeder, Ed Coord, International Medical Education Corporation, 64 Inverness Drive East, Englewood, CO 80112 Tel: (303) 790-8445; (800) 525-8651.

FLORIDA

Mar 1–3. **Clinical Management of the Elderly Patient.** 15 Cat 1 credits. Lake Buena Vista. Info: Clinical Management/HEC, The American Geriatrics Society, c/o The Health and Education Council, 7201 Rossville Blvd, Baltimore, MD 21237. Tel: (301) 686-3610.

Mar 7–10. **Teaching Conference in Clinical Cardiology.** 29 Cat 1 credits. Bal Harbour. Info: Michael S Gordon MD, PHD, University of M School of Medicine (D41), PO Box 016960, Miami, FL 33101. Tel: (305) 547-6491.

Mar 16–18. **Recent Advances in Pediatric Lung Diseases.** 20 Cat 1 credits. Sarasota. Info: Rayna Dutton, CME Coordinator, University at Buffalo, SUNY, Department of Pediatrics, School of Medicine, Children's Hospital, 219 Bryant St, Buffalo, NY 14223. (716) 878-7630.

GEORGIA

Apr 26–29. **American College of Physicians Annual Session.** Atlanta. Info: Annual Session Division, American College of Physicians, 4200 Pine St, Philadelphia, PA 19104. Tel: (215) 243-1200.

HAWAII

Mar 5–9. **Advances in Adolescent/Young Adult Medicine Symposium.** 20 Cat 1 credits. Maui. Info: Institute for CME, Hurley Medical Center, One Hurley Plaza, Flint, Michigan 48502. Tel: (313) 257-9142.

Mar 24–31. **Hawaiian Cruise Seminar on Diagnostic Imaging.** 16 Cat 1 credits. Info: Hawaiian Cruise Seminar on Diagnostic Imaging, PO Box 18057, Rochester, NY 14618. Tel: (716) 461-1332.

ILLINOIS

Mar 19–21. **Pediatric Dermatology.** 20 Cat 1 credits. Chicago. Info: The Cook County Graduate School of Medicine, 707 South Wood St, Chicago, IL 60612. Tel: (312) 733-2800.

LOUISIANA

Apr 29–May 5. **International Seminar on Leprosy.** Info: W. Felton Ross, American Leprosy Missions, One Broadway, Elmwood Park, NJ 07407. Tel: (201) 794-8650.

MARYLAND

Mar 8–10. **Update on Cardiac Catheterization.** 20 Cat 1 credits. Bethesda. *Mar 25–29.* **Annual Scientific Session of the American College of Cardiology.** Bethesda. Info: Ronald J Sanchez, Dir of Comm, American College of Cardiology, 9111 Old Georgetown Rd, Bethesda, MD 20814. Tel: (301) 897-5400.

Mar 26–Apr 6. **Clinical Cytopathology for Pathologists.** 147 Cat 1 credits. Baltimore. Info: John K Frost, MD, 604 Pathology Building, The Johns Hopkins Hospital, Baltimore, MD 21205. Tel: (301) 955-3522.

MASSACHUSETTS

Mar 30–Apr 1. **Decision-Making and Women's Health: Toward Calibration Between Physicians and Patients.** Boston. Info: Roxanne Hurley, Massachusetts Medical Society, 1440 Main St, Waltham, MA 02254. Tel: (617) 893-4610.

Apr 2–4. **Genetics and the Law.** 18 Cat 1 credits. Info: American Society of Law & Medicine, 765 Commonwealth Ave, Boston, MA 02215. Tel: (617) 262-4990.

Apr 19–20. **Advanced Trauma Life Support Course.** Info: Theresa Gaffney, RN, Beth Israel Hospital, Rabb 322, 330 Brookline Ave, Boston, MA 12215. Tel: (617) 735-4228.

MICHIGAN

Apr 12–15. **Clinical Applications of Alcoholism Research.** Detroit. Info: Claire Osman, American Medical Society on Alcoholism, 733 Third Ave, New York, NY 10017. Tel: (212) 986-4433.

NEW JERSEY

Apr 9–13. **Developmental-Behavior Disorders Update.** 28 Cat 1 credits. Teaneck. Info: Mrs Julie Nixon, Hackensack Medical Center/ICD, Johnson Hall, 30 Prospect Ave, Hackensack, NY 07601. Tel: (201) 441-2410.

NEW MEXICO

Mar 23–27. **Biofeedback In Perspective.** Albuquerque. Info: Biofeedback Society of America, 4301 Owens St, Wheat Ridge, CO 80033. Tel: (303) 422-8436.

(*continued on page 26A*)

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OKLAHOMA

Mar 4–9. **Critical Care Medicine Course.** 50 Cat 1 credits. Oklahoma City. Info: Mrs Jean McKean, Critical Care Medicine Course, University of Oklahoma Health Sciences Center, PO Box 26901, Oklahoma City, OK 73190. Tel: (405) 271-5904.

TEXAS

Apr 6–7. **Cervical Neoplasia.** Houston. Info: Office of Conference Services, Box 131, MD Anderson Hospital and Tumor Institute, 6723 Bertner Ave, Houston, TX 77030. Tel: (713) 792-2222.

Apr 12–15. **Family Practice Recertification Review.** 24 Cat 1 credits. San Antonio. Info: Medical School Continuing Education Services, The University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Drive, San Antonio, TX 78284. (512) 691-6295.

Apr 26–27. **Ethics for a Categorical Institution.** Houston. Info: Office of Conference Services, Box 131, University of Texas, M D Anderson Hospital and Tumor Institute, 6723 Bertner Ave, Houston, TX 77030. Tel: (713) 792-2222.

WASHINGTON, DC

Apr 27–28. **Pediatric Tracheostomy Care—New Trends in Medical, Nursing, and Home Management.** Info: Pat Hennessy, RN or Kenneth Grundfast, MD, Dept of Otorhinolaryngology, Children's Hospital National Medical Center, 111 Michigan Ave, NW, Washington, DC 20010. (202) 745-2159.

AROUND THE WORLD

ARGENTINA

Apr 2–6. **Congress of Pediatric Gastroenterology and Nutrition and Congress of the Latin American Society for Pediatric Gastroenterology and Nutrition.** Info: Jorge Ortiz, MD, Sarmiento 1562, 4 to piso "E" CP 1042, Buenos Aires, Argentina.

References:

1. Stone PH, Turi ZG, Muller JE: Efficacy of nifedipine therapy for refractory angina pectoris. *Am Heart J* 104:672-681, September 1982.
2. Antman E, Muller J, Goldberg S, et al: Nifedipine therapy for coronary-artery spasm: Experience in 127 patients. *N Engl J Med* 302:1269-1273, June 5, 1980.

BRIEF SUMMARY
PROCARDIA® (nifedipine) **CAPSULES** For Oral Use

INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in those patients are incomplete

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See Warnings.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving PROCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PROCARDIA and a beta blocker, but the possibility that it may occur with PROCARDIA alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In PROCARDIA treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for PROCARDIA to be washed out of the body prior to surgery.

Increased Angina: Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Beta Blocker Withdrawal: Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients, usually receiving a beta blocker, have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See Warnings.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Drug Interactions: Beta-adrenergic blocking agents: (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing PROCARDIA to avoid possible over- or under-digitalization.

Carcinogenesis, mutagenesis, impairment of fertility: When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose.

Pregnancy: Category C. Please see full prescribing information with reference to teratogenicity in rats, embryotoxicity in rats, mice and rabbits, and abnormalities in monkeys.

ADVERSE REACTIONS: The most common adverse events include dizziness or light-headedness, peripheral edema, nausea, weakness, headache and flushing each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Additionally, the following have been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, diarrhea, constipation, inflammation, joint stiffness, shakiness, sleep disturbances, blurred vision, difficulties in balance, dermatitis, pruritus, urticaria, fever, sweating, chills, and sexual difficulties. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

Laboratory Tests: Rare, mild to moderate, transient elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted, and a single incident of significantly elevated transaminases and alkaline phosphatase was seen in a patient with a history of gall bladder disease after about eleven months of nifedipine therapy. The relationship to PROCARDIA therapy is uncertain. These laboratory abnormalities have rarely been associated with clinical symptoms. Cholestasis, possibly due to PROCARDIA therapy, has been reported twice in the extensive world literature.

HOW SUPPLIED: Each orange, soft gelatin PROCARDIA CAPSULE contains 10 mg of nifedipine PROCARDIA CAPSULES are supplied in bottles of 100 (NDC 0069-2600-66), 300 (NDC 0069-2600-72), and unit dose (10x10) (NDC 0069-2600-41). The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

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PROCARDIA can mean the return to a more normal life for your patients—having fewer anginal attacks,[1] taking fewer nitroglycerin tablets,[2] doing more, and being more productive once again.

Side effects are usually mild (most frequently reported are dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%).

Quotes from an unsolicited letter received by Pfizer from an angina patient. While this patient's experience is representative of many unsolicited comments received, not all patients will respond to Procardia nor will they all respond to the same degree.

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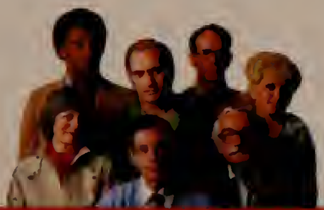

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Please see PROCARDIA *brief summary on adjoining page.*

SYMPOSIUM

"New York State and the Offshore Medical Schools"
Tuesday, March 13, 1984
Downstate Medical Center, Brooklyn, New York

9:00 A.M.	Greetings.	Donald J. Scherl, M.D., President, Downstate Medical Center
9:10 A.M.	Introduction.	Alan Blum, M.D., Editor, *New York State Journal of Medicine*
9:20 A.M.	An Overview of New York State and the Offshore Medical Schools.	Pascal James Imperato, M.D., M.P.H. & T.M., Professor and Chairman, Department of Preventive Medicine and Community Health, Downstate Medical Center
9:30 A.M.	The Historical and Theoretical Basis for the Current Policy of the New York State Board of Regents.	Steven Jonas, M.D., M.P.H., Associate Professor, Department of Community and Preventive Medicine, Health Sciences Center, SUNY, Stonybrook
9:50 A.M.	New York State's Program for Evaluating Offshore Medical Schools.	Thomas Monahan, Associate Executive Secretary, New York State Board of Medicine
10:10 A.M.	Offshore Medical Students: Problems For Hospitals, Medical Schools and Physicians in New York State.	Richard N. Pierson, Jr., M.D., Professor of Clinical Medicine, Columbia University, College of Physicians and Surgeons, Chairman, Committee on Medical School Relations, Medical Society of the State of New York
10:30 A.M.		Questions and Answers.
11:00–11:30 A.M.		Coffee Break.
11:30 A.M.	Clinical Clerkships—Problems and Solutions.	Jackson W. Riddle, Ph.D., M.D., Consultant, Medical Society of the State of New York
11:50 A.M.	Offshore Medical School Graduates—A View From The New York City Health and Hospitals Corporation.	Jo Bouffard, M.D., Vice President, New York City Health and Hospitals Corporation
12:10 P.M.	Experience With American Students From Foreign Medical Schools In Clinical Clerkships.	Alvin I. Kahn, M.D., Director, Medical Affairs and Medical Education, Brookdale Hospital and Medical Center, Clinical Associate Dean, Downstate Medical Center
12:30 P.M.	Panel Discussion.	Questions and Answers

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No Fee. To be held in the First Floor Auditorium, Downstate Medical Center. For Information contact the Department of Preventive Medicine and Community Health, 450 Clarkson Avenue, Brooklyn, N.Y. 11203 or call (212) 270-1056.

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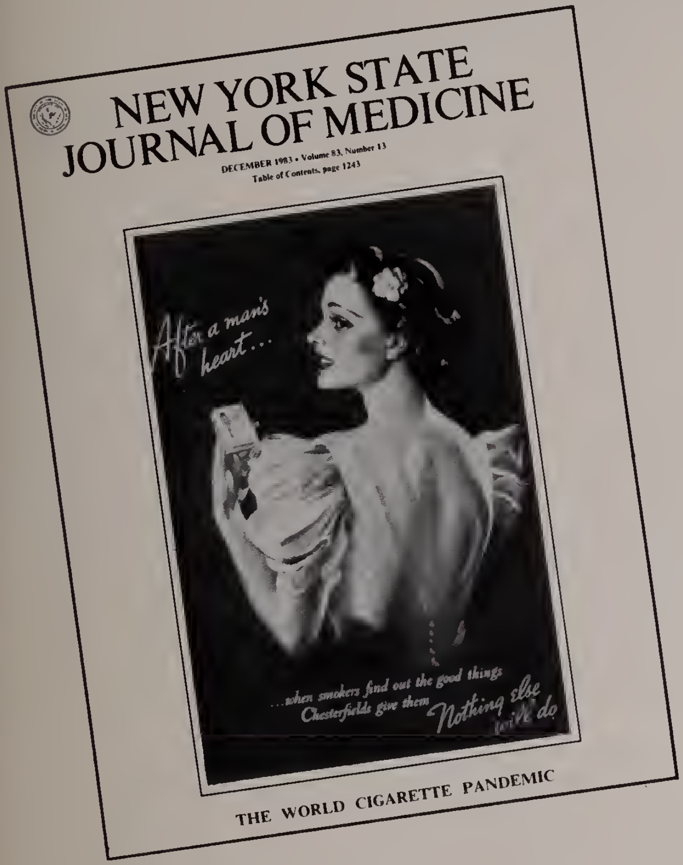

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Dosage may be increased to 160 mg once daily, as needed, to achieve optimal control. INDERAL LA should not be used in congestive heart failure, sinus bradycardia, cardiogenic shock, heart block greater than first degree, and bronchial asthma. Please see next page for further details and brief summary of prescribing information.

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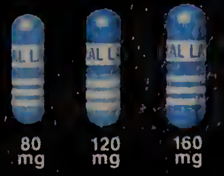
(PROPRANOLOL HCl) LONG ACTING CAPSULES



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JUST ONCE EACH DAY FOR SIMPLIFIED CORE THERAPY IN ANGINA

ONCE-DAILY

INDERAL® LA

(PROPRANOLOL HCl) LONG ACTING CAPSULES

Just once each day...

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)*

INDERAL® LA brand of propranolol hydrochloride **(Long Acting Capsules)**

DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.

CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain.

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma; 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL

WARNINGS. CARDIAC FAILURE Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible)

> IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS Beta blockade may mask certain clinical signs of hyperthyroidism Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. *General.* Propranolol should be used with caution in patients with impaired hepatic or renal function INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure Patients should be told that INDERAL may interfere with the glaucoma screening test Withdrawal may lead to a return of increased intraocular pressure

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DRUG INTERACTIONS Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy Pregnancy Category C INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose

There are no adequate and well-controlled studies in pregnant women INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: INDERAL is excreted in human milk Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia, congestive heart failure, intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System. lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia, visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory bronchospasm

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval

HYPERTENSION—*Dosage must be individualized* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved The usual maintenance dosage is 120 to 160 mg once daily In some instances a dosage of 640 mg may be required The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized.* The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily The dosage may be increased gradually to achieve optimum migraine prophylaxis If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued It may be advisable to withdraw the drug gradually over a period of several weeks

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

*The appearance of INDERAL LA capsules is a registered trademark of Ayerst Laboratories

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Classified Advertising

PHYSICIANS WANTED

ABIM CERTIFIED with subspecialty in gastroenterology/cardiology, preferrably certified to join medical group practice in South Shore Long Island, New York. Send resume to P.O. Box 504, Cedarhurst, N.Y. 11516.

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ANESTHESIOLOGIST: Upstate New York, Acute medical/surgical hospital with active medical staff looking for board eligible or certified anesthesiologist. Excellent quality of life and setting. Interested candidate should send resume and economic expectations to Dept. 324, c/o NYSJM.

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ALEXANDRIA BAY, N.Y., General Surgeon. Space available in new medical office building. Guaranteed income. Fully accredited fifty bed community hospital in the beautiful Thousand Islands region of upstate New York. Two hours from Syracuse and Toronto. Contact Joseph Kehoe, Administrator, Noble Hospital, Alexandria Bay, N.Y. 13607. Phone (315) 482-2511.

SOUTHERN CALIFORNIA—We are seeking experienced specialists and general practitioners for our 28 facilities in Los Angeles and Orange Counties. Located in close proximity to major teaching centers, we offer the opportunity of continued professional development and rewarding clinical practice in association with 370 full-time physicians. Compensation and benefits are excellent including paid vacation, educational leave, sick leave, and retirement; insurances included are malpractice, life, disability, medical and dental. Send CV to: Director/Physician Recruitment CIGNA Healthplans of California, 700 N. Brand Blvd., Suite 500, Glendale, CA 91203.

FOR CHILDREN'S CO-ED Overnight camp—July–August 1984—2 or 4 week periods Camp Echo located in the lower Catskill Mountains of N.Y. State—350 children ages 6–16. Private room and bath facilities family accommodated. Write: Camp Echo, P.O. Box 255, Roslyn, N.Y. 11576 or call between 9:00 a.m. and 6:00 p.m. (516) 742-2679.

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INTERNIST—WANTED to join group of three others. Excellent 100 bed facility with well trained staff. Fine sports and recreational facilities. Send CV to Adirondack Internal Medicine Group RFD Box 410D, Saranac Lake, NY 12983. (518) 891-3845.

INTERNIST, BOARD CERTIFIED, or Eligible, wanted for modern out-patient facility in Nassau County which specializes in the detection of High Blood Pressure. Physician will utilize the most up-to-date diagnostic tests & equipment and be responsible for the implementation of both drug and non-drug related therapy. To be considered for this attractive opportunity offering an excellent salary and company-paid benefits, please call in confidence, Personnel Director (212) 486-8958.

SCHOOL PHYSICIAN, FULL TIME, 10 months (September-June), excellent gross. Available immediately. Medical consultant to school district. An equal opportunity employer. Send resumes to: Personnel Department, White Plains City School District, 5 Homeside Lane, White Plains, New York 10605.

PRACTICES WANTED

DERMATOLOGIST, well trained and with excellent references, seeks to purchase active dermatology practice within 100 miles of New York City. Reply Dept. 328, c/o NYSJM.

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OPHTHALMOLOGIST, BOARD Certified F.A.C.S, F.I.C.S., desires to purchase ophthalmology practice in Manhattan. Strictly confidential. Reply to Dept. 306, c/o NYSJM.

INTERNAL MEDICINE. Boston and NYC university hospital trained internist seeking small group practice 1–1½ hours from NYC in NY, CT, NJ. Boston U MD Cum Laude, 1981. ABIM eligible and available July 1984. David L. Oshin, M.D., 30 W 61st St., Apt. 6D, NYC 10023.

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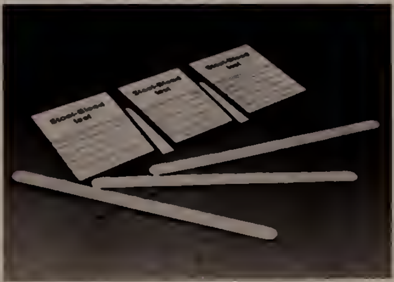
MISCELLANEOUS—

PHYSICIANS SIGNATURE LOANS TO $50,000. Take up to 7 years to repay with no pre-payment penalties. Competitive fixed rate, with no points, fees or charges of any kind. Use for taxes, investment, consolidation or any other purpose. Prompt, courteous service. Physicians Service Association, Atlanta GA. Serving MD's for over 10 years. Toll-free (800) 241-6905.

50,000 people will be saved from colorectal cancer this year. You can save one.

Save yourself! Colorectal cancer is the second leading cause of cancer deaths after lung cancer. More than 90% of colorectal cancers occur equally in men and women past age 50. Early detection provides the best hope of cure. That's why if you're over 50, you should take this simple, easy slide test of your stool every year. This Stool Blood Test kit is chemically treated to detect hidden blood in the stool and can be done at the time of your periodic health examination so your doctor will know the results.

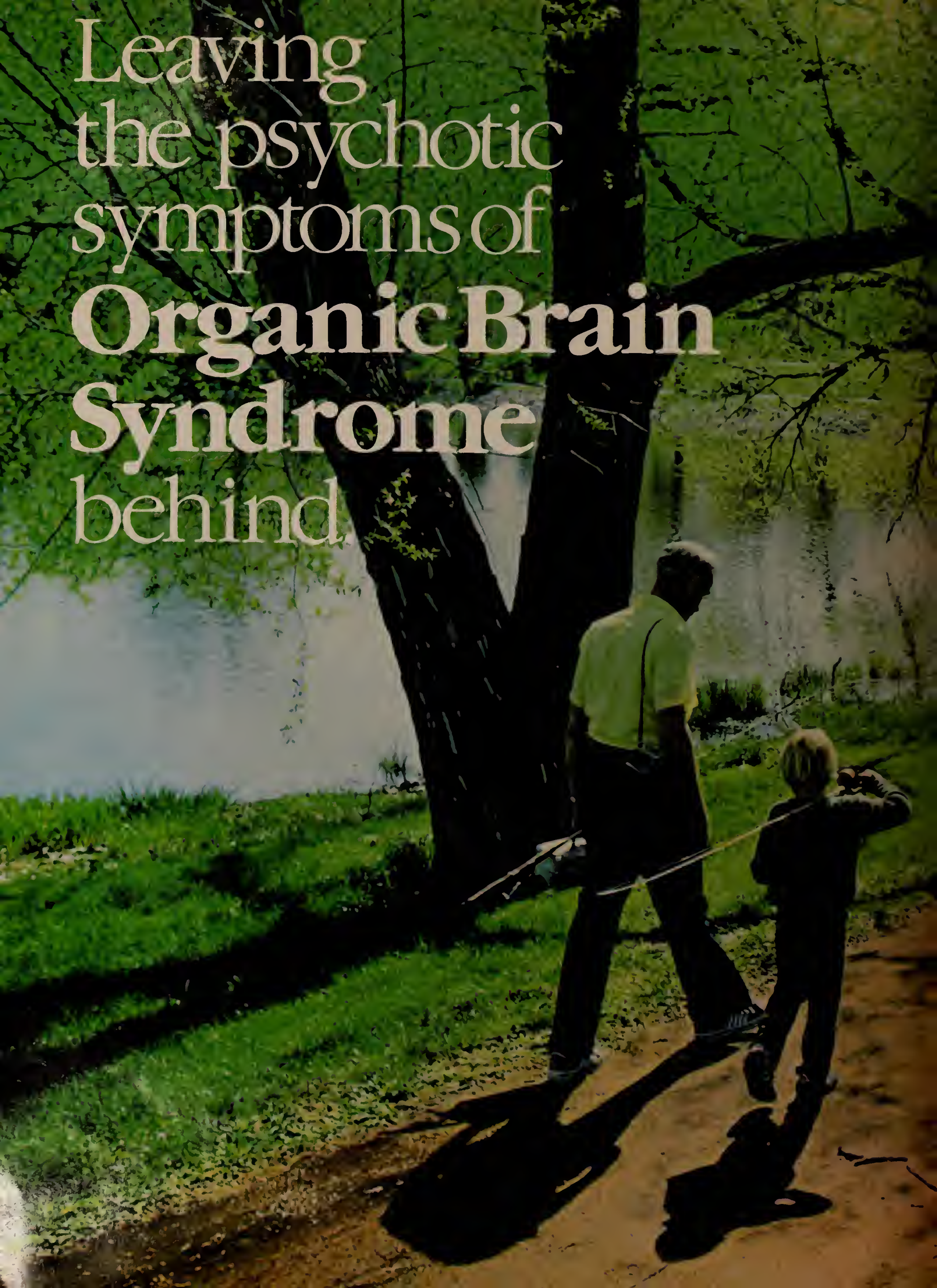


The presence of hidden blood usually indicates some problem in the stomach or bowel, not necessarily cancer. Positive tests must be followed by further testing to find out what the problem is.

Other tests for colorectal cancer you should talk to your doctor about: digital rectal exam (after age 40); the procto test (after age 50). It is important to report any personal or family history of intestinal polyps or ulcerative colitis, and any change in your bowel habits, which could be a cancer warning signal.

The American Cancer Society wants you to know.

AMERICAN CANCER SOCIETY®


Leaving the psychotic symptoms of
Organic Brain Syndrome
behind.

Effective

Treatment with Navane can produce improvement in psychotic symptoms such as hallucinatory behavior and unusual thought content as well as hostility, disorientation and depressive mood,[1,2] leaving the elderly patient more alert[2] and better able to participate in the activities of family life.

Well tolerated

Navane is generally well tolerated by elderly patients. Excessive sedation or drowsiness has been reported, but is uncommon.[1] Anticholinergic effects[3] and hypotension[4,5] are reported, but rarely. Should they occur, extrapyramidal symptoms can usually be readily controlled.

Navane®

(thiothixene) (thiothixene HCl)

Capsules 1 mg, 2 mg, 5 mg, 10 mg, 20 mg
Concentrate 5 mg/ml Intramuscular 2 mg/ml, 5 mg/ml

See following page for a brief summary of prescribing information

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at the forefront of psychopharmacology

Navane®

(thiothixene) (thiothixene HCl)

References: 1. Util TM, Unverdi C. Wohlrade J, et al: Drug therapy of psychosis associated with organic brain syndrome. Presented as a Scientific Exhibit at the American Public Health Association Centennial, Atlantic City, New Jersey, November 12-16, 1972. 2. Katz MM, Util TM: Video methodology for research in psychopathology and psychopharmacology. *Arch Gen Psychiatry* 31:204-210, 1974. 3. Ketai R. Psychotropic drugs in the management of psychiatric emergencies. *Postgraduate Medicine* 58 87-93, 1975. 4. Birkett DP, Hirschfield W, Simpson GM. Thiothixene in the treatment of diseases of the senium. *Curr Ther Res* 14 775-779, 1972. 5. Data on file at Roerig.

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Navane® (thiothixene) Capsules: 1 mg, 2 mg, 5 mg, 10 mg, 20 mg

(thiothixene hydrochloride) Concentrate: 5 mg/ml, Intramuscular: 2 mg/ml, 5 mg/ml

Contraindications: Navane (thiothixene) is contraindicated in patients with circulatory collapse, comatose states, central nervous system depression due to any cause, and blood dyscrasias Navane is contraindicated in individuals who have shown hypersensitivity to the drug. It is not known whether there is a cross-sensitivity between the thioxanthenes and the phenothiazine derivatives, but the possibility should be considered.

Warnings: *Usage in Pregnancy*—Safe use of Navane during pregnancy has not been established. Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus. Animal reproduction studies and clinical experience to date have not demonstrated any teratogenic effects.

In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen. (See Precautions.)

Usage in Children—The use of Navane in children under 12 years of age is not recommended because safety and efficacy in the pediatric age group have not been established

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol.

Precautions: An antiemetic effect was observed in animal studies with Navane, since this effect may also occur in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumor.

In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered concurrently.

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with other CNS depressants other than anticonvulsant drugs.

Though exhibiting rather weak anticholinergic properties, Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving atropine or related drugs.

Use with caution in patients with cardiovascular disease.

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine lenticular pigmentation has been noted in a small number of patients treated with Navane for prolonged periods) Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenic purpura), and liver damage (jaundice, biliary stasis) have been reported with related drugs

Undue exposure to sunlight should be avoided. Photosensitive reactions have been reported in patients on Navane.

Neuroleptic drugs elevate prolactin levels, the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Intramuscular Administration—As with all intramuscular preparations, Navane Intramuscular should be injected well within the body of a relatively large muscle The preferred sites are the upper outer quadrant of the buttock (i.e. gluteus maximus) and the mid-lateral thigh.

The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-thirds of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.

Adverse Reactions: *Note.* Not all of the following adverse reactions have been reported with Navane (thiothixene). However, since Navane has certain chemical and pharmacologic similarities to the phenothiazines, all of the known side effects and toxicity associated with phenothiazine therapy should be borne in mind when Navane is used

Cardiovascular effects. Tachycardia, hypotension, lightheadedness, and syncope. In the event hypotension occurs, epinephrine should not be used as a pressor agent since a paradoxical further lowering of blood pressure may result. Nonspecific EKG changes have been observed in some patients receiving Navane These changes are usually reversible and frequently disappear on continued Navane therapy The incidence of these changes is lower than that observed with some phenothiazines The clinical significance of these changes is not known.

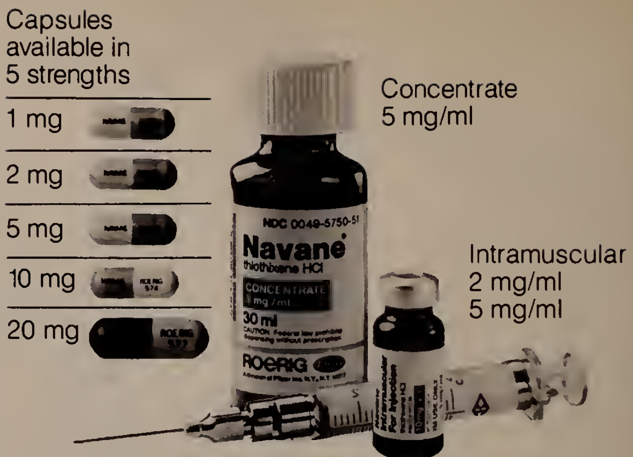
CNS effects Drowsiness, usually mild, may occur although it usually subsides wtih continuation of Navane therapy The incidence of sedation appears similar to that of the piperazine group of phenothiazines, but less than that of certain aliphatic phenothiazines. Restlessness, agitation and insomnia have been noted with Navane (thiothixene). Seizures and paradoxical exacerbation of psychotic symptoms have occurred with Navane infrequently

Hyperreflexia has been reported in infants delivered from mothers having received structurally related drugs.

In addition, phenothiazine derivatives have been associated with cerebral edema and cerebrospinal fluid abnormalities

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia, and dystonia have been reported Management of these extrapyramidal symptoms depends upon the type and severity Rapid relief of acute symptoms may require the use of an injectable antiparkinson agent. More slowly emerging symptoms may be managed by reducing the dosage of Navane and/or administering an oral antiparkinson agent

Persistent Tardive Dyskinesia: As with all antipsychotic agents tardive dyskinesia may appear in some patients on long term therapy or may occur after drug therapy has been discontinued The risk seems to be greater in elderly patients on high-dose therapy, especially females The symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities



There is no known effective treatment for tardive dyskinesia, antiparkinsonism agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear

Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, the syndrome may be masked.

It has been reported that fine vermicular movements of the tongue may be an early sign of the syndrome and if the medication is stopped at that time, the syndrome may not develop.

Hepatic effects: Elevations of serum transaminase and alkaline phosphatase, usually transient, have been infrequently observed in some patients. No clinically confirmed cases of jaundice attributable to Navane (thiothixene) have been reported.

Hematologic effects: As is true with certain other psychotropic drugs, leukopenia and leukocytosis, which are usually transient, can occur occasionally with Navane. Other antipsychotic drugs have been associated with agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopenia.

Allergic reactions: Rash, pruritus, urticaria, photosensitivity and rare cases of anaphylaxis have been reported with Navane. Undue exposure to sunlight should be avoided. Although not experienced with Navane, exfoliative dermatitis and contact dermatitis (in nursing personnel) have been reported with certain phenothiazines.

Endocrine disorders: Lactation, moderate breast enlargement and amenorrhea have occurred in a small percentage of females receiving Navane. If persistent, this may necessitate a reduction in dosage or the discontinuation of therapy Phenothiazines have been associated with false positive pregnancy tests, gynecomastia, hypoglycemia, hyperglycemia, and glycosuria.

Autonomic effects. Dry mouth, blurred vision, nasal congestion, constipation, increased sweating, increased salivation, and impotence have occurred infrequently with Navane therapy Phenothiazines have been associated with miosis, mydriasis, and adynamic ileus.

Other adverse reactions: Hyperpyrexia, anorexia, nausea, vomiting, diarrhea, increase in appetite and weight, weakness or fatigue, polydipsia and peripheral edema.

Although not reported with Navane, evidence indicates there is a relationship between phenothiazine therapy and the occurrence of a systemic lupus erythematosus-like syndrome.

NOTE: Sudden deaths have occasionally been reported in patients who have received certain phenothiazine derivatives In some cases the cause of death was apparently cardiac arrest or asphyxia due to failure of the cough reflex In others, the cause could not be determined nor could it be established that death was due to phenothiazine administration.

Dosage and Administration: Dosage of Navane should be individually adjusted depending on the chronicity and severity of the condition. In general, small doses should be used initially and gradually increased to the optimal effective level, based on patient response.

Some patients have been successfully maintained on once-a-day Navane therapy.

Usage in children under 12 years of age is not recommended because safe conditions for its use have not been established

Navane Intramuscular Solution: Navane For Injection—Where more rapid control and treatment of acute behavior is desirable, the intramuscular form of Navane may be indicated It is also of benefit where the very nature of the patient's symptomatology, whether acute or chronic, renders oral administration impractical or even impossible.

For treatment of acute symptomatology or in patients unable or unwilling to take oral medication, the usual dose is 4 mg of Navane Intramuscular administered 2 to 4 times daily. Dosage may be increased or decreased depending on response. Most patients are controlled on a total daily dosage of 16 to 20 mg. The maximum recommended dosage is 30 mg/day An oral form should supplant the injectable form as soon as possible. It may be necessary to adjust the dosage when changing from the intramuscular to oral dosage forms Dosage recommendations for Navane (thiothixene) Capsules and Concentrate appear in the following paragraphs.

Navane Capsules: Navane Concentrate—In milder conditions, an initial dose of 2 mg three times daily. If indicated, a subsequent increase to 15 mg/day total daily dose is often effective.

In more severe conditions, an initial dose of 5 mg twice daily.

The usual optimal dose is 20 to 30 mg daily If indicated, an increase to 60 mg/day total daily dose is often effective. Exceeding a total daily dose of 60 mg rarely increases the beneficial response.

Overdosage: Manifestations include muscular twitching, drowsiness, and dizziness. Symptoms of gross overdosage may include CNS depression, rigidity, weakness, torticollis, tremor, salivation, dysphagia, hypotension, disturbances of gait, or coma

Treatment: Essentially is symptomatic and supportive. For Navane oral, early gastric lavage is helpful. For Navane oral and Intramuscular, keep patient under careful observation and maintain an open airway, since involvement of the extrapyramidal system may produce dysphagia and respiratory difficulty in severe overdosage. If hypotension occurs, the standard measures for managing circulatory shock should be used (I.V. fluids and/or vasoconstrictors.)

If a vasoconstrictor is needed, levarterenol and phenylephrine are the most suitable drugs Other pressor agents, including epinephrine, are not recommended, since phenothiazine derivatives may reverse the usual pressor action of these agents and cause further lowering of the blood pressure.

If CNS depression is present and specific therapy is indicated, recommended stimulants include amphetamine, dextroamphetamine, or caffeine and sodium benzoate. Stimulants that may cause convulsions (e.g picrotoxin or pentylenetetrazol) should be avoided Extrapyramidal symptoms may be treated with antiparkinson drugs

There are no data on the use of peritoneal or hemodialysis, but they are known to be of little value in phenothiazine intoxication.

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NEW YORK STATE
JOURNAL OF MEDICINE

March 1984 • Volume 84, Number 3

COMMENTARIES

Needle aspiration biopsy of a thyroid mass

Needle aspiration biopsy of thyroid nodules, as described by Silver et al in this issue of the *Journal*, plays a complementary role in identifying the etiology of a thyroid nodule and in distinguishing between those lesions that can be managed by observation and suppression and those that require excision for diagnosis or treatment. The final decision must be based upon the history, physical findings, and clinical milieu in which the nodule occurs. A long-standing thyroid mass in an elderly woman would be much more likely to represent a benign adenomatous goiter than would a mass in a young man.

Thyroid scans are useful in identifying nodules that are at greater risk of being malignant by virtue of their nonfunction as opposed to those that exhibit uptake of radioiodine. Some surgeons would not biopsy "functioning" nodules because of the negligible incidence of malignancy. If one is to forego a biopsy of such a nodule, the phenomenon of disparate imaging must be recognized. Most thyroid scans are carried out with technetium 99m which measures the "trapping" function of the thyroid epithelium whereas radioiodide (iodine 123, iodine 131) measures trapping and organification. Approximately 5% of of tumors that are "cold" by radioiodide scan may show some trapping function with technetium and thus appear to be "warm." For this reason, scanning with iodine 123 is preferable to the use of technetium 99m. An alternative is to "rescan" with iodine 123 lesions that are functioning by technetium scan.

Histopathologic characteristics of the thyroid can be studied using a cutting needle biopsy technique (Vim-Silverman or True-Cut) with removal of a core of tissue for routine microscopy or by aspiration of cells through a fine or large bore needle (#22-19) and examination of their cytologic characteristics. The aspiration biopsy technique is more acceptable to patients and has a lower morbidity. Both techniques are useful in the differentiation of adenomatous goiter, cysts, thyroiditis, papillary cancer, and undifferentiated and medullary cancer. In contrast to the experience of the authors, most cytopathologists and pathologists cannot differentiate between a follicular adenoma and a follicular adenocarcinoma. Such differentiation requires complete excision of the lesion.

The limitations of this technique are related to the procurement of a representative sample of the thyroid lesion (small and substernally located nodules are constraints) and appropriate interpretation. The overall results of the authors are consistent with the findings of others. One distinct advantage of the aspiration biopsy technique using a fine needle is that the procedure can be easily repeated should there be an inadequate specimen or should the patient's course be inconsistent with the initial clinical impression.

We have employed a technique similar to that of the authors except that a 1-mL tuberculin syringe has been used. After aspirating the "nodule" the needle is capped and the syringe and needle are sent intact to the cytopathologist. The cytopathologist is responsible for making and processing the slide. Few unsatisfactory preparations have resulted with such an approach.

The authors recommend "surgical exploration" for lesions that are considered by cytopathologic criteria to be questionable or suspicious. It must be emphasized that an incisional biopsy is ill advised. For a definitive diagnosis such lesions require excision of the entire mass with a margin of surrounding thyroid parenchyma. This is best accomplished by a lobectomy.

Overall, needle aspiration biopsy of thyroid nodules with an evaluation by a competent cytopathologist represents a distinct advance in the evaluation of a dominant thyroid mass. To be noted, however, is that pathology is an interpretative rather than an exact science, and the findings must be considered in regard to the overall clinical status of the patient.

COLIN G. THOMAS, JR, MD
Department of Surgery
University of North Carolina
School of Medicine
Chapel Hill, NC 27514

A concern about thrombolytic reperfusion

The safety and efficacy of new forms of treatment usually are determined after repeated clinical trials and extensive experience. Such was the case with approval by the Food and Drug Administration of streptokinase-induced thrombolytic reperfusion delivered by the intracoronary route in the treatment of arterial occlusion. Yet the enthusiasm for intracoronary thrombolysis has occurred in spite of major unresolved concerns.[1]

The unusual experience reported by Hollander et al in this issue of the *Journal* is one of many complications that have been reported with use of thrombolytic therapy for evolving transmural myocardial infarction. Cardiorrhexis occurs in myocardial infarction, but usually quite late. It involves small infarcts and occurs via multiple small pathways instead of large discrete areas of perforation through the anterior wall as in the case report in this issue.[2] Mathey et al[3] have reported hemorrhage into the area of infarction, Fishbein et al[4] have found this to be the case following experimentally induced infarction but there was no extension beyond the area of infarction after reperfusion. Why did this cardiac rupture occur? Was the infarction older than the authors could have clinically suspected? Did this catastrophic event occur as part of the natural history of the infarct (which would relegate thrombolytic reperfusion to the role of innocent bystander)? Could the autopsy findings have been a consequence of cardiopulmonary resuscitation? We do not know. However, this report raises the important question of whether or not streptokinase reperfusion may induce myocardial rupture in the presence of softened, infarcting tissue.

To incriminate streptokinase, a mechanism for this type of outcome must be explained. The reader cannot know if rupture and thrombolytic infusion are directly tied together or whether this case happens to be an aberration. Nevertheless, this report should not be overlooked, as these investigators are not alone in their finding of myocardial rupture associated with thrombolytic therapy.[5] If fatalities can be directly attributed to streptokinase infusion, then researchers, clinicians, and patients must be forewarned about this potential problem.

MARCUS A. DeWOOD, MD
Director of Cardiovascular Research
Sacred Heart and Deaconess Medical Centers
800 West Fifth Ave.
Spokane, WA 99210

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Three new acronyms: PPS, DRG, PRO

The American Medical Association (AMA) sponsored a conference on peer review organizations (PROs) and the prospective payment system (PPS) for hospitals on September 19 and 20, 1983 in Washington, DC. The speakers included Senator David Durenberger (Chairman of the Senate Subcommittee on Health) and representatives from the AMA, Health Care Financing Administration, Health Standards and Quality Bureau, and the New Jersey, California, Massachusetts and Missouri State Medical Societies.

The intent of the conference was to acquaint physicians with the recent federally mandated PPS for hospitals based on 468 Diagnosis-Related Groups (DRGs) and to provide relevant information regarding contracts for Peer Review Organizations (PROs). The latter came into place as part of the Tax Equity and Fiscal Responsibility Act passed in Congress in 1982 and is a new concept in peer review intended to replace the PSRO program.

The AMA's position, according to Executive Vice-President James Sammons, MD, is that it is not opposed to PPS and DRGs but feels that the government should not implement new programs until they have been tried on a limited basis. The government did not follow this course in the case of DRGs. Fifty million Americans are now covered by Medicare and Medicaid. Health care costs are now 10.5% of the gross national product—a startling figure when one recalls that in 1960 health costs were 5.3% of the gross national product. In 1982 $322 billion was spent on health care and 27% of this was paid by the federal government—two thirds of which was for hospital care. Hospital costs rise about 12% a year, and it is estimated that between 1988 and 1990 the Medicare fund will go bankrupt.

The federal government is attempting to meet the health crisis by two means: regulation and competition. The government is aiming at means to improve efficiency, put physician providers at risk, curtail unnecessary utilization, and encourage less costly alternatives (home care, hospices, etc). It must be remembered that the DRG system pays only the operating costs—not capital costs, education costs, bad debts, long term care, psychiatric and children's rehabilitation hospital care. There may be special payments for cancer hospitals (defined as those with 50% of all patients having a diagnosis of cancer), sole community hospitals, and referral centers (defined as having 60% of their patients from out-of-state or at least 50 miles distant). There will be some exceptions made in the case of rural vs urban hospitals and area differences in hospital wages. Also, allowances shall be made for "outliers" (defined as exceeding the DRG length of stay by 20 days or by 1.94 S.D.'s, whichever is less).

Alfred A. Alessi, MD, an AMA delegate from the New Jersey State Medical Society, discussed the impact of DRGs in his state. He emphasized that the physician is the most important cog in the wheel but that there is little data available at this time to show whether the system has saved money. However, certain patterns have emerged: physician efficiency has improved as evidenced by better progress notes on the charts; record room coding is more exact; more data is available to the hospital administration; and there are fewer full-time physicians on hospital staffs. Some data indicate an increase in liability cases because patients are being discharged too early. Everything that goes wrong is currently blamed on the physicians, and the system has pitted physician against physician and hospital against hospital. Three hospitals have closed their doors and there is a lack of funding for many essential programs in those that have survived. In short, the DRG system has all the seeds for divisiveness among the hospital's administration, their boards, their medical staffs, employees, patients, unions, and insurance companies.

The intent of the PRO is to bring about more competition and the DRGs have made the PROs different from the PSRO concept. The DRGs under the PRO system introduce a new payment system concentrating on whether the DRG coding assignment was correct, whether the outliers warrant special treatment, and whether an unnecessary admission has occurred. The PRO emphasis is to reduce admissions from previous inadequate treatment, to assure completeness of treatment, to reduce unnecessary surgery and avoidable post-operative complications, and to reduce avoidable deaths. Out-patient procedures are encouraged, admission monitoring is mandated, and overall admissions and invasive procedures are expected to be reduced. The government talks about a "sentinel effect." (Just being there will change behavior). Physician sanction will be speeded up since the Health Care Finance Administration must react within 120 days—a far cry from the PSRO experience.

Which PROs will be successful?

1. PROs that are working with a hospital that has developed a respect for the peer review concept.
2. PROs with widespread physician support.
3. PROs in which there is an established peer review process in place with incentives and sanctions.
4. PROs in areas with a stable hospital staff.
5. PROs in areas with an excess of physicians and areas in which there is a high hospital occupancy rate.
6. PROs with a good data system, a network with other data bases, and where there are physicians trained in data analysis.
7. PROs with a strong administrative staff, i.e. executive director, data, nursing and finance personnel.

Have we learned anything from the PSRO experience? We have been made aware that it is difficult to work with the federal government. Congress is unpredictable and the regulations and funding are in constant flux. This relationship calls to mind the old saw that "the lion and the lamb may lie down together but the lamb won't get much sleep." We have learned that review systems are not going to go away and that good work in this arena is not always rewarded. The good PSROs had enough impact to allow the program to survive, but the important lesson is that the medical profession must retain the major voice in peer review—we must insist that judgement about acceptable medical care is expertise only a physician possesses.

JOHN T. PRIOR, MD
Medical Director
PSRO of Central New York
Community General Hospital
Broad Road
Syracuse, New York 13215

Asbestos in New York State

In recent years, there has been growing public and professional concern about the malignant disorders associated with asbestos exposure. It is well established that the incidence of malignant mesothelioma is substantially increased in humans exposed to this mineral, as is the incidence of lung cancer (primarily in those who also smoke cigarettes).[1] One recent study estimates that approximately 19,000 cases of mesothelioma and 55,000 cases of lung cancer will occur in the United States in men with histories of nontrivial occupational exposure to asbestos.[2] An increased frequency of gastrointestinal cancer and peritoneal mesothelioma has also been described,[1] although these observations are surrounded by many uncertainties. Although malignant mesothelioma is a rare disorder (overall average incidence of about 0.45 per 100,000 population in New York State (excluding New York City),[3] it is rapidly lethal and we do not know with certainty whether or not its incidence is increasing. In New York State (excluding New York City), there was no apparent increase from 1973 through 1978,[3] but this observation might be misleading. The diagnosis of mesothelioma may be difficult, especially when a detailed occupational history is not obtained. Even the presence of asbestos bodies in the lungs is not diagnostic of malignant mesothelioma. In this issue of the *Journal* Tagliamonti et al and Ramaswamy et al bring to our attention still another potential difficulty in establishing a diagnosis. The neoplasm can occur in unusual anatomic sites such as pericardium, appendix, tunica vaginalis, and the testes. In these situations diagnosis becomes ever more difficult.

Is there a safe level of asbestos exposure, and is the important consideration related to the type and physical state of the mineral? The risk of mesothelioma is considerably higher among individuals exposed to crocidolite asbestos (blue asbestos) when compared to the chrysotile type.[4] In experimental animals, however, the pulverization of chrysotile fibers results in a higher incidence of this disorder.[5]

Should the future use of asbestos be banned in view of the many questions that currently exist? And with what do we replace it? Admittedly, there are other naturally occurring minerals with fibrous structures but they do not possess the insulation properties, heat stability, and weavability of asbestos. Some fibers such as zeolite (Al_2O_3) possibly have the same tumorigenic properties as asbestos.[6] Accordingly, great care must be taken in identifying a "safe" substitute. At the very least we must evaluate fibers that are larger than asbestos. In addition, banning asbestos will probably have little effect on the cancer incidence of those exposed in the past.

Given these morbid facts, what can responsible physicians and other groups do? We and the public must become more aware of the many past and present uses of asbestos. This is particularly important in our "do-it-yourself" era when many old homes are being remodeled. Since exposure at an early age is probably an important factor in developing mesothelioma, particular attention should be given to children. Although the overall sex ratio for this malignancy is 2.2, the potential risk for females should not be overlooked.[3] The sex ratio for peritoneal mesothelioma approximates unity,[3] and some evidence suggests that women might be at increased risk of nonoccupational exposure to asbestos.[7] Tight industrial hygiene controls should be rigidly enforced in workplaces where asbestos is used. The more hazardous types of asbestos such as crocidolite should probably be banned.

On the larger public health scale, programs that identify and monitor workers exposed both in the past and present should be instituted. At the very least this should reduce the incidence of asbestosis, and might even prevent some cases of lung cancer and mesothelioma, although this is less certain. Some preliminary efforts to identify high-risk areas in New York State have already been initiated. A study of the epidemiologic patterns of malignant mesothelioma in New York suggested that certain highly populated industrialized counties (such as Erie, Nassau, and Suffolk) in close proximity to major waterways appear to have higher average incidence rates than does the state (excluding New York City).[3] Construction and electrical heating system workers are particularly involved. In many rural counties, farmers, talc miners, and paper workers are at high risk for this disorder.[3] As of April 1, 1982, asbestosis became a reportable disease to the New York State Health Department's Occupational Lung Disease Registry. In addition, as of January 1, 1983, identifying information about employees who work with this mineral must be reported annually to the New York State Health Department. It is hoped that information obtained from these systems will identify and educate potentially high-risk groups throughout the state.

NICHOLAS J. VIANNA, MD
Director, Division of Health
Risk Control
New York State Health Department
Albany, NY 12237

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Chemical weapons: a question of morality

Since 1982 the US State Department has claimed that the Soviet Union used chemical weapons (including nerve agents, phosgene, nitrogen mustard, and lewisite) in its invasion of Afghanistan, killing 3,042 people in 47 separate attacks between 1979 and 1981. The State Department has also charged that in Laos and Cambodia in 1981 the Soviet Union directed its Vietnamese allies in the use of a biological weapon, allegedly a toxin produced by the fungus *Fusarium* popularly referred to as "yellow rain."

Use of chemical or biological weapons is a violation of the Geneva protocol of 1925 and the 1972 Convention on Biological Weapons. Regrettably, the protocol contains no provision for verification or enforcement. Although the United States and the Soviet Union are committed to a "no first use" of chemical weapons, each country maintains a stockpile in order to be able to retaliate in the event of a violation of the commitment.[1] Most reports suggest that the Soviet stockpile is enormous and that its troops are well-trained in the use of chemical weapons. In contrast, in the wake of the deaths in 1968 of 6,300 sheep downwind of the Army's nerve gas testing center in Utah, President Nixon halted open-field testing of such weapons; no new chemical agent has since been added to the American arsenal. In 1972, Nixon also ordered an end to the manufacture of biological weapons—including organisms for plague, tularemia, botulism, anthrax, and Venezuelan equine encephalitis.[1]

The United States had not acted on the Geneva protocol of 1925 until Nixon sent it to the Senate for ratification in 1969. It was finally approved in 1975, but not before the Army proposed the production of a new generation of chemical weapons. In 1980, the Reagan administration took up the Army's position by calling for a chemical weapons modernization program. The first step in the $6 to $7 billion build-up would be a $124.4 million outlay for the "Bigeye" binary bomb—155 mm projectiles containing two inert chemicals that combine in flight to form a poison gas, one inhalation of which is sufficient to block acetylcholinesterase at every nerve ending in the body, causing convulsions and asphyxiation.

The General Accounting Office, an investigative unit of Congress, advised against the funding of nerve gas because of doubts about design, performance, and cost. Last year the House of Representatives voted 258 to 165 against approving the resumption of chemical weapon manufacture. But twice, by single vote margins, the Senate voted to recommend production. Although a House-Senate committee subsequently rejected the administration's plan to resume production of nerve gas, the Army's research and development of chemical weapons continues, and the issue is likely to be raised again this year. The move against resumption of manufacture is significant in light of the committee's approval of nearly all of the administration's $252.5 billion defense budget, including funds for the MX and Pershing II missiles and the B-1 bomber.

Discussing and comparing the morality, destructive potential, or deterrent capability of various weapons of war may at first seem inappropriate or irrelevant for a journal of medicine. So much has been written about the horrific risks and senselessness of a nuclear arms race that it would seem futile or tiresome to raise an equal alarm over a weapon that would kill far fewer people. Moreover, at a time of talk about ever more grandiose space-based "Star Wars" weapons systems, mention of nerve gas may conjure up anachronistic strategies out of the era of trench warfare. It is even possible that the serendipitous benefits to mankind of chemical weapons, such as their role in the study of the sense of smell[2] or, as reviewed by Dauber in this issue of the *Journal*, their selective tumor-fighting activity in lymphoproliferative disorders, might suggest to some that continued research and development is still worth the risk.

But one cannot avoid noticing the irony in the statement by Secretary of State Schultz about the Soviet Union's "cynical disregard for international law and agreements" and his call for an end to the use of chemical and toxic weapons, while at the same time advocating a major build-up of American supplies of these poisons. Such comments are also ironic at a time when the nation is agonizing over its own use of herbicides in Vietnam and the longterm consequences of toxic chemical and nuclear wastes.

Is nerve gas really less moral a weapon than a nuclear bomb—or, for that matter, a gun and bullets? Yes. The nuclear Pandora's box has forced us to accept the concept of nuclear weapons as a deterrent force and the foolishness of the thought of a "limited" nuclear war. Guns and bullets can at least be said to be intended for military targets. Chemical and biological weapons, on the other hand, are more likely to affect civilians than soldiers. Matthew Melesen, PhD, a biochemist and authority on chemical weapons, estimates the ratio of civilian to military casualties to be 20 to 1.[3]

The Army argues that nerve gas is a deterrent by forcing the enemy to "suit up" in protective gear and thus drain troop performance.[4] But one nerve gas, GB, or Sarin, carried by the wind has the potential to inflict casualties for days in an unprotected population. Another agent, VX, is released as a viscous fluid that coats surfaces and remains toxic for weeks.[3] Although proponents of nerve gas manufacture, such as New York's Senator Alphonse D'Amato, point out that West Germany lies exposed to a Soviet chemical attack, no European country, including West Germany, is willing to store the proposed new supply of American-made nerve gas, or to train its troops in the use of the substance.

Death and suffering are unimaginable to most healthy persons, and so it is the duty of physicians to promote a reverence for life and to help reduce the risk of suffering and premature death. The loss of freedom is also an abstract thing, and the end of a democratic, pleuralistic society would be tantamount to death for many.

Yet the acknowledgment of nuclear weapons as a deterrent should not mean the acceptance of other weapons of torture and suffering merely to keep up with the Soviets. As the *Philadelphia Inquirer* noted in an editorial last year,

> Why yield the high ground? Why take the onus off the Soviet Union?
>
> The way to stop [the use of chemical and biological weapons] is not to start yet another spiral in the arms race. The way to stop is not to start producing even more terrible weapons whose strategic value is dubious, whose primary usefulness (if that's the word) is against civilians. The way to stop is to negotiate from the strength of the high ground.

Ending the development and production of chemical and biological weapons should be an important objective for everyone concerned about preserving a sane and humane world.

ALAN BLUM, MD

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Address correspondence to Editor, New York State Journal of Medicine, *420 Lakeville Road, Lake Success, NY 11042. Letters should be typed double-spaced and include the signature, academic degree, professional affiliation, and address of each author. Preference is given to letters not exceeding 450 words, and every effort will be made to assure prompt publication. All letters are personally acknowledged by the Editor.*

Brain stem ischemia and syncope

TO THE EDITOR: In reading the article "Syncope in a general hospital population" by Howard E. Gendelmann et al (*NY State J Med* 1983; 83:1161–1165), I note that no mention was made of brain stem ischemia as an etiologic factor. This possible cause of syncopal episodes warrants serious attention, since it could well be a mechanism to account for sudden death. Such deaths are often misdiagnosed as being due to acute myocardial infarction.

ANTHONY M. IMPARATO, MD
New York University Medical Center
New York, NY 10016

In reply: We appreciate Dr Imparato's raising of one of the most perplexing issues in the etiology of syncope, that of cerebrovascular insufficiency. While we did include neurovascular causes of syncope in our study (transient ischemic attacks were diagnosed in 6 percent of our patients), we remain uncertain about the role played by brain stem ischemia in the etiology of isolated syncopal episodes.

In a recent prospective study with stringent diagnostic criteria[1] a diagnosis of vertebrobasilar insufficiency as a cause of syncope was not accepted, unless the episode was accompanied by other symptoms of vertebrobasilar ischemia. Barnett[2] also has noted that it is unwise to attribute loss of consciousness to brain stem ischemia when syncope is the sole symptom. Mazurek[3] has noted agreement with the developing concept that neurologic causes for syncope are very rare.

We currently accept a diagnosis of vertebrobasilar insufficiency for syncope, if a prolonged episode of loss of consciousness is accompanied by other symptoms (e.g., diplopia, vertigo, hemiparesis) of brain stem ischemia. We suspect, however, that this area shall remain a source of controversy, as it is exceedingly difficult to prove or disprove a diagnosis of transient brain stem ischemia as a cause of isolated syncope.

MARK LINZER, MD
North Central Bronx Hospital
Montefiore Medical Center
Bronx, New York 10467

HOWARD GENDELMAN, MD
Division of Neurology
The Johns Hopkins Medical Institutions
Baltimore, Maryland 21205

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Dr Jack Lovelock

TO THE EDITOR: I am researching a biography of the late Dr Jack Lovelock (1910–1949), the New Zealand Olympic athlete, whose last years were spent at the Hospital for Special Surgery, New York, and who died in New York. I would be pleased to hear from any former colleagues or from anyone who knew him well.

JAMES McNEISH
Flat 8, Gloucester House
Worcester Place
Oxford 0X1 2HB, England

Jack E. Lovelock won the 1,500 meter run at the 1936 Olympic Games.

Declining incidence of rheumatic heart disease

TO THE EDITOR: In referring to rheumatic heart disease Brinsfield states, "Yet, we can look with pride at the declining incidence of this disease and know prevention is working."

In 1946 and 1947 I analyzed the 15-year statistics of the cardiac clinic at Lenox Hill Hospital and noted a steady decrease in the number and percent of patients who had rheumatic heart disease since 1932. I very much doubt that the doctors had anything to do with this; it was before streptococci were known as the etiologic agent, and long before we had any of the sulfa drugs that first appeared in 1937.

JOHN V. WALLER, MD
130 East 77 St.
New York, NY 10021

In reply: The declining incidence of acute rheumatic fever is an accepted fact by the majority of epidemiologists and pediatric cardiologists in this country. In an individual area, there can be a decline in acute rheumatic fever or in the number of cases of residual rheumatic heart disease over a period of time. If one looks at the entire country and the published statistics, a true decline in new cases of rheumatic fever did not occur until after the widespread use of penicillin for the treatment of streptococcal infections. In reviewing retrospective studies, one realizes that in the 1930s and 1940s many patients with mitral regurgitation were labeled as having residual rheumatic heart disease when in reality they had Barlow's syndrome. A few doubtless had mitral regurgitation secondary to silent myocardial infarction. The major problem in diagnosis in the pediatric age group during those years was that murmurs from the aortic and mitral valves were called rheumatic in origin until the knowledge of congenital heart disease became widespread. I recall seeing numerous patients in the 1940s and 1950s who were followed in rheumatic heart disease clinics and were later recognized as having congenital heart disease.

The major reports in this country concerning a decrease in residual rheumatic heart disease lagged behind the decreased incidence of acute rheumatic fever. Certainly in the South we were still seeing a large number of new cases even in the 1960s. The most dramatic decline in acute rheumatic fever occurred in the 1970s. I believe this is related more closely to the availability of treatment for the majority of children needing medical care and the widespread use of penicillin for acute pharyngitis than to other factors.

DOROTHY BRINSFIELD, MD
Emory University School of Medicine
Atlanta, GA 30322

Granular cell tumor of the esophagus

TO THE EDITOR: Granular cell myoblastoma or Abrikossoff's tumor of the esophagus is a rare entity.[1] Since the lesion was first described by Abrikossoff in 1926, fewer than 35 cases involving the esophagus have been described.[2,3] It arises also in other locations, most commonly in the tongue, skin, and subcutaneous tissues.[2]

Case report. A 42-year-old woman came to Queens Hospital Center complaining of dysphagia. Her difficulty in swallowing solid foods began one year before, and within the past three months had progressed to difficulty in swallowing liquids. The patient denied any anorexia or weight loss. Her past medical history and physical examination were unremarkable. Barium swallow was performed and revealed a 3 cm × 2.5 cm, well circumscribed intramural lesion with smooth borders in the distal esophagus (Fig 1). This lesion appeared to be consistent with a leiomyoma. On endoscopic examination a large mass in the lateral wall of the distal esophagus just proximal to the gastroesophageal junction was observed. A biopsy sample was not taken for fear that hemorrhage might result. At surgery a 6.25-cm mass with a broad base and smooth borders was found connected to the lateral wall of the distal esophagus. The entire mass with its adherent mucosa was excised. The patient did well after surgery.

Gross examination of the specimen showed a well encapsulated yellowish-pink mass covered by esophageal mucosa. Histologic examination revealed strands and clumps of large polyhedral cells with small uniform nuclei. The cytoplasm contained large quantities of eosinophilic granules (Fig 2). The overlying squamous epithelium exhibited hyperplasia. These findings were compatible with a histologic diagnosis of granular cell myoblastoma.

Discussion. Granular cell myoblastoma of the esophagus is a rare benign tumor.[1] The exact origin of this granular cell tumor is still controversial. It was believed to be of mesenchymal and Schwann cell origin, but most authorities now favor a neurogenic origin.[4-6]

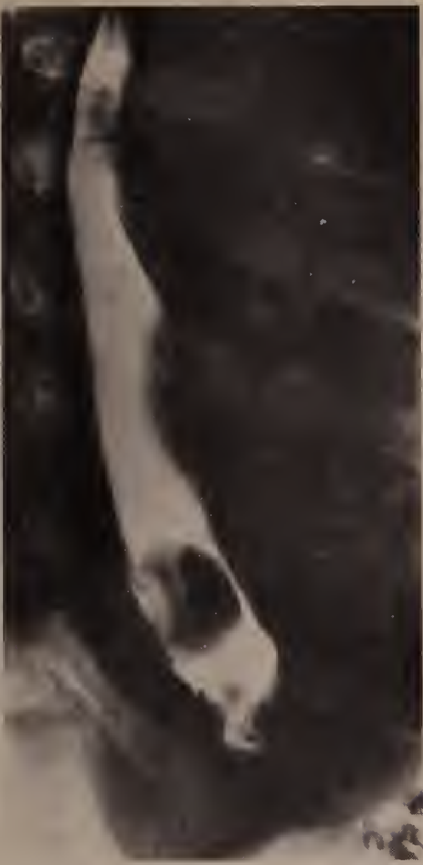

FIGURE 1. Barium swallow reveals a mass in the lower end of the esophagus with well-defined borders.

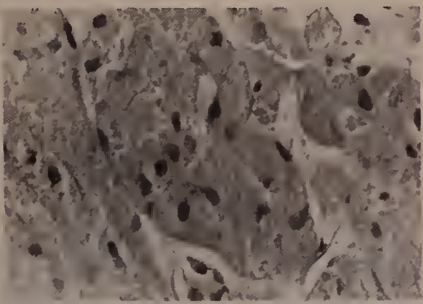

FIGURE 2. Photomicrograph of excised specimen shows large polyhedral cells with small nuclei. Cytoplasm contains large quantities of eosinophilic granules (×400).

Although most commonly seen in the skin, subcutaneous tissues, breast, tongue, pharynx, stomach, and female genital tract, this tumor may also be found in any organ system of the body.[1,5,7,8] There appears to be a predilection for young black women in the third to fourth decades of life.[6,9] In 25% of reported cases, lesions were multiple.[3,5] Whether these multiple lesions represent multifocal origin or metastasis from an original lesion has not yet been determined.

Patients with esophageal granular cell tumors tend to be asymptomatic or have dysphagia, as in the case reported here.[6,10,11] In the majority of cases the lesion is picked up as an incidental finding during the workup of the patient, or even at autopsy.[3] The upper part of the esophagus is most frequently the site of the lesion, followed by the distal third and lastly by the middle third of the esophagus.[2,3] Radiographic appearance is nonspecific. Barium swallow usually reveals a smooth, well circumscribed intramural filling defect that is usually first diagnosed as a leiomyoma[3] or other benign lesions such as fibrous lipomas, neurofibromas, or duplication cysts.

The tumor is usually seen through the endoscope as a whitish-yellow elevation with a smooth surface. A number of investigators advise against biopsy for fear of hemorrhage.[10] The treatment of choice is surgical excision of the entire mass. Incompletely excised tumors may recur.[6]

Seen under the microscope, the tumor is characterized by large groups of polyhedral cells with small, dense nuclei. The cytoplasm contains large quantities of eosinophilic granules. At the periphery, tumor cells are usually seen infiltrating the surrounding normal tissue.[10] The vast majority of these lesions are benign; however, a few cases have been described in which the lesion had undergone malignant degeneration.[6,10] Granular cell tumors of the esophagus should be considered in the differential diagnosis of tumors of the esophagus.[6]

KIRAN CHAWLA, MD
LEON ADLER, MD
STEVEN SOBO, MD
LESLIE L. ALEXANDER, MD
Queens Hospital Center Affiliation
82-68 164th Street
Jamaica, NY 11432

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A rambling bullet

TO THE EDITOR: A penetrating bullet wound may produce an unusual diagnostic problem, with the x-ray showing the foreign body in an unexpected location, a considerable distance from the entry site. "Wandering bullets," in the majority of cases, are due to intravascular embolization,[1] while migration of bullets through the GI tract is infrequent.

We present a patient in whom the bullet traversed multiple organs, creating a diagnostic dilemma. Physicians identified an unusual problem that might have ended disastrously were it not for some fortuitous decisions during surgery.

Case report. A 26-year-old man was admitted to Lincoln Medical and Mental Health Center with a posterior gunshot wound of the right chest, inferior to the scapula with no wound of exit. A right tube thoracostomy relieved a tension pneumothorax with complete expansion of the right lung (Figs). Except for bullet fragments at the site of entry, no foreign bodies were visible in the chest. The bullet was seen in the left upper quadrant of the abdomen. There was only a minimal air leak through the chest tube and very little bleeding.

With the diagnosis of a transdiaphragmatic gunshot wound of the abdomen, exploratory celiotomy was performed. There were no diaphragmatic injuries, and the remainder of the exploration was negative except that the bullet was palpated within the lumen of the stomach.

Assuming that the bullet perforated the upper thoracic esophagus, with subsequent migration to the stomach, a fiberoptic esophagoscopy was performed during surgery. An area of contusion without perforation was noted in the proximal esophagus, just below the thoracic inlet.

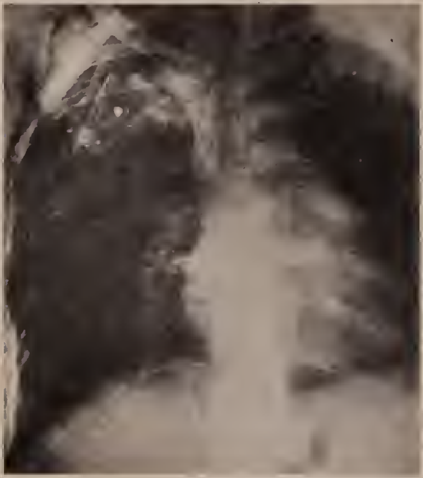
The esophagus was explored through a cervical incision. The endoscopic finding of contusion with no perforation was confirmed. No air leak from the trachea was identified. At this point it was thought that the inflated cuff of the endotracheal tube might be masking a tracheal perforation. The cuff was deflated and, with positive pressure ventilation, a large air leak through a 1-centimeter posterolateral tracheal wound was demonstrated. The laceration was repaired, and the subsequent course of recovery was uneventful.

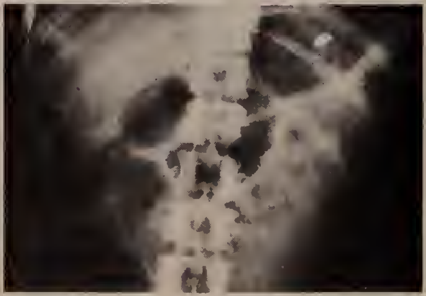
Discussion. In retrospect, it is apparent that the bullet must have entered the trachea, been coughed into the pharynx, and swallowed by the patient prior to radiologic examination. The patient denied awareness of coughing up or swallowing the bullet.

The vast majority of bullets that do not follow a predictable path are deflected by dense structures such as bone. A few aberrant bullets are the result of intravascular embolization. Gastrointestinal,[1,2] tracheobronchial,[3] or urinary[4] migration of bullets appears to be extremely uncommon. A remarkable case of a gunshot wound to the uterus of a pregnant woman in which the fetus, 36 weeks in gestation, apparently swallowed the bullet and passed it through the rectum a few days after birth, was reported by Buchsbaum and Caruso in 1969.[5]

Aside from its unusual nature, this case demonstrates some important principles in the management of penetrating injuries. Firstly, a penetrating wound of the trachea may be masked by the inflated cuff of the endotracheal tube, concealing the perforation. The simple maneuver of deflating the cuff, while administering positive pressure ventilation, will reveal the air leak at the site of injury and facilitate repair.[6] Secondly, as shown by Ledgerwood,[1] it is important to recognize that the patient may expel the bullet spontaneously by the act of coughing, voiding or defecation. If this were to happen prior to admission, no bullet would be detected by radiography. This finding, and the absence of an exit wound, should raise the possibility of spontaneous evacuation of the bullet by the patient through a natural orifice, after it had penetrated a hollow viscus. Finally, unexpected and unexplained findings should alert the surgeon to the presence of occult and unusual injuries.

RAO R. IVATURY, MD
MICHAEL ROHMAN, MD
Department of Surgery
Lincoln Medical and Mental Health
Center and New York Medical College
Bronx, NY 10451





Roentgenograms demonstrating bullet fragments in the right chest and the bullet in the left upper quadrant of the abdomen.

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Cytologic evaluation of thyroid nodules

New criteria for surgery

CARL E. SILVER, MD, RICHARD J. BRAUER, MD, KLAUS SCHREIBER, MD

ABSTRACT **The addition of cytologic evaluation of material obtained by fine needle aspiration to the previously available diagnostic methods for thyroid nodules has greatly improved the physician's ability to select lesions appropriate for surgery. Only about one third of thyroid carcinomas are suspected on the basis of clinical criteria. The remainder are indistinguishable from benign nontoxic nodular goiter. Radioisotope scanning has a high degree of sensitivity, but very low specificity, resulting in a large number of false positives. Needle aspiration cytology has both high sensitivity and virtually 100% specificity. Used in combination with radioisotope scanning, it increases the accuracy of preoperative diagnosis. Ultrasonography is of little value relative to its cost when needle aspiration is employed. Using the new criteria for surgery in nodular goiter, the percentage of malignant tumors in surgical patients on the authors' service has increased from 16% to 35% overall, and from 11% to 24% in patients without clinically obvious carcinoma.**

(NY State J Med 1984; 84:109–112)

INTRODUCTION

For the past four years, needle aspiration biopsies have been employed routinely on our service for the preoperative evaluation of thyroid nodules. The procedure has proved to be a valuable aid in selecting patients for surgery.

Before the advent of needle biopsy, selection of patients with thyroid nodules for surgery was an inexact science. The methods employed included clinical evaluation, radioisotope scanning, and, more recently, ultrasonography. These methods are of value, but reliance on any one or a combination of them failed to identify many malignant thyroid nodules.[1-3] This resulted not only in thyroid surgery on an excessive number of patients with benign nodules, but also in failure to recommend surgery for some patients with nodules that were malignant.

In this study we will evaluate the selection of patients with thyroid nodules for surgery both before and after the routine use of needle aspiration cytology. We will also analyze the effect of this procedure on the ability to identify nodules most likely to be malignant and the consequent change in percentage of malignancies found at operation. New criteria for selection of patients with thyroid nodules for surgery will be outlined.

PATIENTS AND METHODS

A comparison was made between the results of thyroid surgery on our service both before and after routine use of needle aspiration cytology for preoperative evaluation. During the period January 1, 1974, to December 31, 1977, 141 thyroidectomies were performed using currently available clinical and laboratory criteria. In mid-1978, the use of fine needle aspiration biopsy for cytology was introduced onto our service for selected patients. After January 1, 1979, needle aspiration biopsies were employed routinely in almost every patient with nodular goiter. By the end of 1981, needle aspirations had been performed in 178 patients. Of these patients, 104 underwent surgery. The techniques of needle aspiration and method of handling the specimen have already been described.[4]

Results of surgery after cytologic evaluation of thyroid nodules were incorporated into the decision-making process and were compared with results of surgery in 141 consecutive patients operated upon before that time.

RESULTS

Between 1974 and 1977, 141 patients underwent surgery. Criteria employed for selection of these patients were absolute and relative clinical indications, and results of radioisotope scanning. A total of 22 malignancies (16%) were found in 141 surgical patients. Seven malignancies (32%) were obvious on clinical examination. The incidence of malignancy in the remaining nodules was 11% (15 of 134).

Subsequently, needle aspiration biopsies were performed on 178 patients. Diagnosis was confirmed by surgical excision of the lesions in 104 patients. Table I summarizes the surgical findings in these patients. Twenty-two of the biopsy samples had been reported positive for malignancy. All were confirmed malignant at operation. Thirty-seven biopsy specimens had been reported negative for malignancy. Three of these were malignant. Thus, in 59 cases in which the nodules were reported as definitely benign or malignant, there were no false positive biopsies and three (8%) false negatives. Forty-five biopsy specimens were reported in the questionable category. Eleven of these (24.5%) were found to be malignant at operation.

Table II summarizes the biopsy findings in the malignant tumors. The procedure was accurate in identifying papillary, follicular, and mixed papillary-follicular carcinomas. Twenty positive biopsy specimens were obtained in this group, with only four questionable and one negative biopsy sample. The procedure was less successful in identifying Hurthle cell, anaplastic, and medullary carcinomas. In the anaplastic lesions, necrosis interfered with diagnostic accuracy of both needle aspiration and core biopsy specimens in two of three cases.

Thirty of the lesions were found on aspiration to consist predominately of cyst fluid. Eighteen of these disappeared or regressed after aspiration. Surgery was not performed for these. Twelve of the cysts recurred soon after aspiration or yielded positive or questionable biopsy samples, or both. These were excised. One specimen from a cystic

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From the Head and Neck Service, Surgical Division (Dr Silver, Dr Brauer) and the Department of Pathology (Dr Schreiber), Montefiore Hospital and Medical Center, and the Albert Einstein College of Medicine, The Bronx, New York

Based on a presentation at the New York Surgical Society, New York City, November 10, 1982.

Address correspondence to Dr Silver, Chief, Department of Head and Neck Surgery, 111 East 210th St, The Bronx, NY 10467.

TABLE I. Surgical Findings in 104 Cases

Cytologic Findings	No. of Cases	Histologic Findings		
		No. Benign	No. Malignant	% Malignant
Positive	22	0	22	100
Negative	37	34	3	8
Questionable	45	34	11	24.5
Totals	104	68	36	

TABLE II. Distribution of Malignant Tumors by Histologic Type

Histologic Type	No. Cases	Cytologic Findings		
		Positive	Questionable	Negative
Papillary	12	9	2	1
Papillary and follicular	6	4	2	0
Follicular	7	7	0	0
Hurthle cell*	7	2	4	1
Anaplastic	2	0	1	1
Medullary	2	0	2	0
Totals	36	22	11	3

* In this series, all Hurthle cell tumors were considered malignant because the clinical behavior of these lesions cannot be predicted on the basis of histologic type.

lesion contained psammoma bodies and was considered positive. At surgery this was found to be malignant. Of 11 cytologically negative cysts, 10 were benign, whereas one was a cystic Hurthle cell tumor. The overall incidence of malignancy in cystic lesions removed at surgery was 17%.

Needle aspiration biopsy appeared to be less accurate for cystic lesions than for solid lesions, as tumor cells were never recovered from a cystic malignancy either in these primary lesions or in two metastatic cystic thyroid tumors not included in this series.

Seventy patients did not undergo surgery after needle biopsy. Several patients with questionable biopsies refused surgery, and surgery was deferred in others because of unacceptably high risk factors. One patient, with a positive biopsy specimen, had known metastatic breast carcinoma confirmed by cervical lymph node biopsy and did not undergo exploration of the thyroid. The remaining patients who did not undergo surgery had negative biopsy specimens that were consistent with the clinical impression of benign nodules. Three had negative "core" biopsy specimens for confirmation. Although the follow-up period is short, in no patient for whom surgery was not recommended has any evidence of malignancy developed.

Complications of needle aspiration were minimal. There were two instances of tracheal puncture, without sequelae. In both instances oral penicillin was administered for a three-day period immediately after the procedure. Hematoma, transient recurrent nerve paralysis, and pneumothorax, which have been reported following "core" biopsies, did not occur in our patients. There has been no evidence of needle tract implantation of tumor, although the brief follow-up period has not permitted adequate assessment of this possibility.

DISCUSSION

The primary reason for recommending operation for nontoxic thyroid nodules is for diagnosis and treatment of possible malignancy, as well as treatment of any malignancy found. There are other reasons for surgery such as the removal of a bulky disfiguring mass, or the relief of mechanical problems such as obstruction of the airway by a large mediastinal goiter. Atypical follicular adenomata are best removed because of uncertainty as to whether they are completely benign.[5] However, there is little reason to remove colloid nodules, benign cysts, or nodular areas of chronic thyroiditis that have not produced cosmetic or mechanical difficulties. Thus, the main diagnostic problem is to determine the probability of malignancy. Various criteria and procedures may be employed for this. Absolute criteria for surgery are (1) extreme firmness of a predominately noncalcified unilateral mass, (2) ipsilateral vocal cord paralysis, (3) presence of known metastatic disease either in cervical nodes or distant, and (4) obstruction of airway or esophagus. Relative criteria are (1) continued growth of nodule while under observation or suppressive therapy, and (2) history of radiation—particularly early in life. The presence of these criteria are still considered indications for surgery. Absolute criteria such as vocal cord paralysis, known metastatic disease, and the characteristic feel of a hard, infiltrating malignant mass are associated with malignancy in almost 100% of instances and, when present, indicate surgical exploration without regard to the results of other tests and procedures. The relative criteria are less often associated with actual malignancy but, nevertheless, have been rightly considered to be clinical indications for surgery.

In our series of patients who underwent preoperative needle biopsy, there were 36 malignant thyroid nodules. Only 13 (35%) of these were obvious or strongly suspected on the basis of clinical criteria. Twenty-three (64%) were indistinguishable on examination from benign nodular goiters. A similar percentage (40%) of obvious tumors was noted in the series of patients reported from this institution in 1970,[6] as well as the previously mentioned 32% in patients operated upon between 1974 and 1977. Thus roughly two thirds of malignant tumors are not recognizable by clinical criteria, indicating the need for various laboratory tests to help in the selection of patients with thyroid nodules for surgery.

It has been established that thyroid nodules that concentrate iodine poorly are more often malignant than similar lesions with normal or greater than normal function. Nevertheless, the incidence of malignancy in "cold" nodules averages only about 25% or lower.[1,7] Although sensitivity of radioisotope scanning is high, its major weakness is low specificity. Ashcraft and Van Herle[1] evaluated 1,836 radioisotope scans with unequivocal findings and reported sensitivity of 87% but specificity of only 30% in diagnosis of thyroid nodules. Thus the large number of false-positive results from isotope scanning minimizes its effectiveness in avoiding surgery for benign lesions.

The chief value of isotope scintiscanning lies in identifying "warm" or hyperfunctioning nodules, as the incidence of carcinoma in these is extremely low.[8] From the surgeon's point of view, establishment that a nodule is "warm" should stand as a good indication that the lesion is benign, although exceptions to this rule occur.[9] In our patients who underwent needle biopsy, two of the 36 malignant nodules found at surgery were hyperfunctioning. Thus the isotope scan, although of value, is only a rough indication of the possibility of a thyroid nodule being benign or malignant.

Ultrasonography may be employed to establish whether

TABLE III. Comparison of Pre- and Post-aspiration Biopsy Results

Years	Operations	No. Malignant	% Malignant
Before NAB			
1974	52	6	12
1975	35	5	14
1976	23	4	17
1977	31	7	23
Totals 1974-1977	141	22	16
After NAB			
1979	39	16	41
1980	35	9	26
1981	30	11	37
Totals 1979-1981	104	36	35

NAB = needle aspiration biopsy.

a thyroid nodule is predominately cystic or solid. This information is of some value, as malignancy is considerably more likely in solid than in cystic nodules.[10] Nevertheless, the usefulness of this procedure is limited.

As has been reported,[11] we found the diagnosis of cyst to be more accurately established by needle aspiration than by ultrasonography. The 17% incidence of malignancy in cystic lesions selected for surgical removal indicates that the presence of cyst fluid did not rule out malignancy, although the incidence was lower than the 37% incidence of malignancy in solid nodules that were removed at surgery. Ultrasonography may be helpful in choosing the size of needle for aspiration, as a larger needle may be preferred for aspirating cystic lesions than for solid lesions. We have, however, used a 19 gauge needle for all aspirations, finding this diameter needle wide enough to permit evacuation of thick cyst fluid, yet fine enough for atraumatic biopsy of solid lesions.

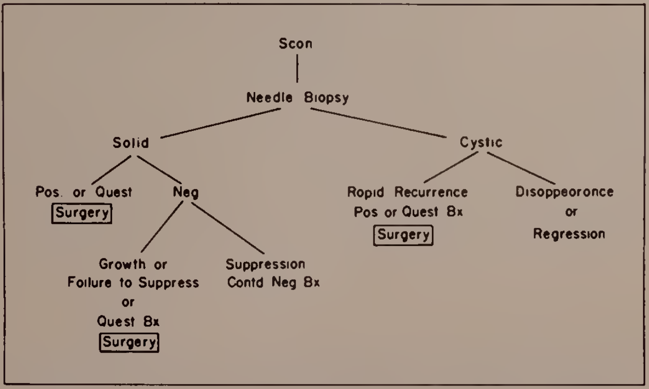
Cytologic evaluation of material recovered by needle aspiration biopsy of thyroid nodules is by far the most accurate method of detecting malignancy in thyroid nodules as well as indicating which nodules have the least probability of proving malignant.[11] In the series reported here, there were no false positives and three false negatives, indicating a sensitivity of 88% and a specificity of 100% for the procedure. These figures compare favorably with the previously mentioned data for radioisotope scanning.

In 59 of the 104 patients results were reported definitively as benign or malignant. The procedure was 95% accurate, in these patients. In 45 patients, or slightly less than half, findings were considered questionable or suspicious, because of the findings of atypical cells, cellular follicular tumor or insufficient material for evaluation. The 24.5% yield of malignancy in this latter group is as high or higher than the yield of malignancy in any series of patients selected for surgery purely on the basis of radioisotope scan findings. If, without regard to other criteria, surgery had been recommended only for patients with positive or questionable cytologic findings, the yield of malignancy in patients operated upon would have been 49%. Three malignancies, however, would have been missed, indicating that needle biopsy cannot be used as the exclusive criterion for surgery in nodular goiter. Clinical factors and judgment must be weighed in with the cytologic findings to determine which nodules should be excised.

Table III summarizes our experience with surgery for thyroid nodules before and after the routine employment of needle aspiration biopsy. During the four-year period from 1974 through 1977, 141 patients underwent surgery for thyroid nodules. Twenty-two (16%) malignant tumors were found. During the three years from 1979 through 1981, 36 (35%) malignant tumors were found in 104 patients who underwent surgery. The difference is striking. (These 104 patients do not correspond exactly to the 104 preoperative needle biopsy patients. Ten needle biopsies were performed in 1978. Four of the patients underwent surgery, and two lesions were found to be malignant. Coincidentally, four of the patients operated upon from 1979 through 1981 did not have preoperative needle biopsies. Two of these patients had malignant lesions. Thus the number of patients and the number of malignancies is the same in both groups.) In addition to avoiding surgery in many patients with benign lesions, the needle biopsy disclosed malignant conditions in several patients who would not have been selected for surgery using previous criteria. Among these were two patients with "warm" nodules and several instances of carcinoma in patients with multinodular adenomatous goiters. The percentage of malignancy in patients without clinically obvious carcinoma was 25% (23 of 91).

A method of incorporating needle biopsy findings with other criteria may now be outlined. All patients with absolute clinical criteria, and most patients with relative criteria, for malignancy should undergo surgical exploration of their thyroid nodules, regardless of the test results. Ultrasonography is an optional procedure that is of little benefit relative to its cost, as the needle aspiration itself will provide the same information. Nevertheless, ultrasonography is completely noninvasive and may be helpful in delineating nodules that are difficult to palpate.

All patients should undergo both radioisotope scanning and needle aspiration biopsy. For hyperfunctioning nodules, surgery is recommended only for patients with positive biopsies. Cytologically negative or questionable lesions should be observed, unless clinical indications for removal are present or subsequently develop. Management of hypofunctioning nodules is outlined in the figure. By aspiration, the nodule is determined to be either solid or cystic.



Process for selecting patients for surgery.

When, after evacuation of a cystic nodule, the lesion disappears or regresses significantly and remains so throughout a prolonged follow-up period, surgery is not recommended. When a cystic lesion recurs soon after aspiration, particularly when it is more than 3 cm in diameter, or when cytologic results are positive or in the moderately to strongly suspicious category, surgery is recommended.

For solid hypofunctioning nodules, surgery is recommended when results of cytologic studies are reported as positive or questionable. When cytology is negative, the nodule is observed and biopsied again at various intervals. Thyroid hormone may be administered for TSH suppression.[12] When the nodule continues to grow or fails to be suppressed, or when repeat needle biopsy yields a positive or questionable result, surgery is recommended.

Good judgment and proper interpretation of data are essential. Close follow-up and repetition of biopsies are the best insurance against missing a malignant tumor. Needle aspiration is not a substitute for surgery. Nevertheless, it is a valuable diagnostic procedure that, when employed appropriately, can greatly improve the ability of the surgeon both to identify patients with thyroid malignancy and to safely avoid surgery when it is not required.

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Outpatient hypospadias repair

TERRY W. HENSLE, MD, KEVIN A. BURBIGE, MD

ABSTRACT **Over an 18-month period, 40 consecutive patients with subcoronal hypospadias underwent hypospadias repair as outpatients. Only those patients with subcoronal lesions and without chordee were included in this series. The mean age at the time of repair was three years with a range of 1.2 to nine years. The average length of hospitalization was eight hours and the overall complication rate was 6%. The majority of the patients underwent a MAGPI (Meatal Advancement Glanduloplasty Incorporated) hypospadias repair, the technical simplicity and reliability of which make it an effective surgical procedure.**

(NY State J Med 1984; 84:112–113)

INTRODUCTION

Hypospadias is a congenital anomaly of the urethra which occurs in some form with a frequency of five to seven per thousand live male births. The majority (85%) of these patients will have distal hypospadias.[1] More proximal forms of hypospadias such as midshaft, penoscrotal junction or perineal hypospadias occur much less frequently.

Distal forms of hypospadias usually cause little functional disability either in childhood or later life. The surgical correction of these more distal forms of hypospadias must therefore provide not only excellent cosmetic and functional results but must also be associated with virtually no morbidity for the child. In an effort to find a simple, safe, and effective method of distal hypospadias repair, surgeons performed hypospadias repair on 40 children, as outpatients, with subcoronal hypospadias. The majority of these children underwent repair using the MAGPI (Meatal Advancement Glanduloplasty Incorporated) technique as described by Duckett.[2]

PATIENTS AND METHODS

Study group. Forty boys aged 1.2 to 9 years with subcoronal hypospadias without chordee were operated upon at the Babies Hospital, Columbia-Presbyterian Medical Center. Their average age was 3 years, and 35 of the 40 patients were uncircumcised. All patients were treated on an outpatient basis. The average length of hospital stay was eight hours and only two patients required overnight hospitalization.

Technique. The initial step in the MAGPI procedure is meatal advancement. This is accomplished using a midline longitudinal incision from the upper edge of the hypospadiac meatus to the distal point of the glans groove (Fig 1).

Suturing the proximal and distal aspects of the incision together creates a Heineke-Mikulicz transverse closure of a vertical incision. This in effect enlarges and advances the meatus (Fig 2). Attention is then directed to the redundant dorsal hood which

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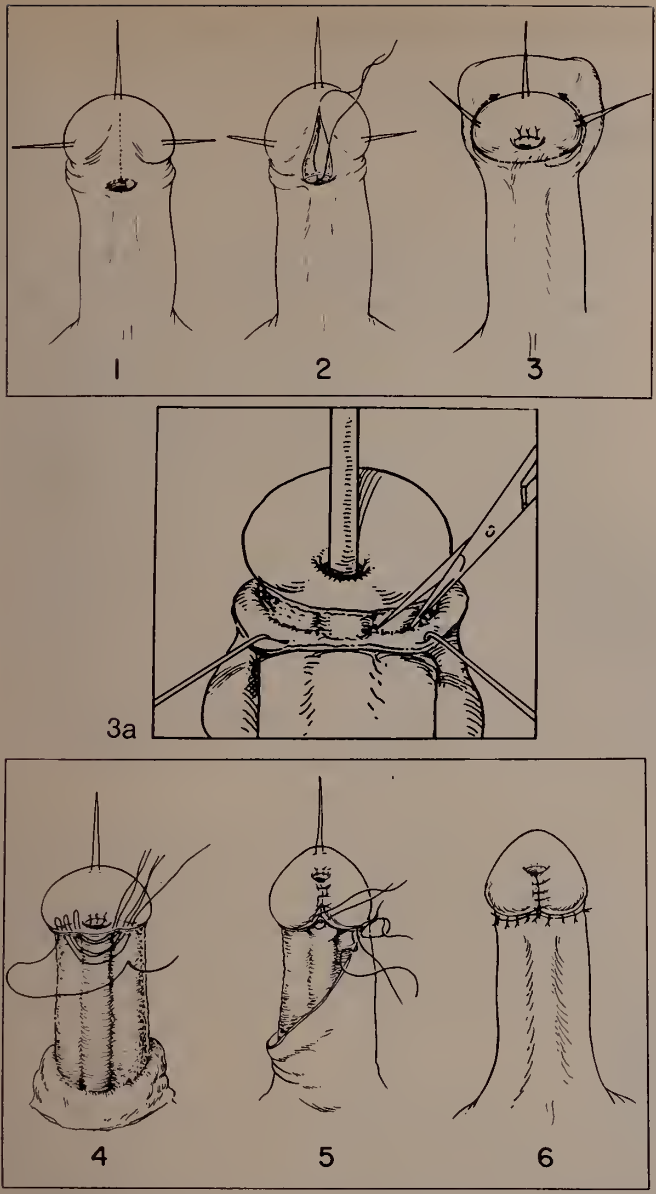
From the Division of Pediatric Urology, Babies Hospital, Columbia-Presbyterian Medical Center, New York, New York.

Address correspondence to Dr Hensle, Director, Division of Pediatric Urology, Babies Hospital, Columbia-Presbyterian Medical Center, 3959 Broadway, New York, NY 10032.



(1) Vertical incision into glans. (2) Upward advancement of meatus. (3) Circumferential incision around glans in order to deglove shaft. (3a) Careful dissection of skin off urethra. (4) Closure of glans penis after release of skin chordee over urethra. (5) Reapproximation of shaft skin. (6) Final appearance.

is incised via a circumferential incision made 5 mm from the coronal edge (Fig 3). The ventral skin overlying the urethra is extremely thin and meticulous dissection is mandatory in order to prevent injury to the urethra (Fig 3a). After adequate mobilization of skin along the entire shaft has been accomplished, glandular approximation is carried out by bringing the edges of the glans penis together in the midline (Fig 4). This maneuver creates a conical glans around and proximal to the advanced meatus (Fig 5). The redundant foreskin is then excised and sleeve reapproximation of shaft skin can be accomplished (Fig 6). A compression dressing is applied for four to six hours and removed before the patient is discharged.

RESULTS

All patients have been observed for at least six months following their surgical repair. Thirty-eight of the 40 patients in this group have had excellent cosmetic and functional results. One patient in the series developed a subcoronal fistula at the point where his urethra was entered during the difficult separation of the ventral skin from the very thin distal urethra, resulting in disruption of the repair at 10 days. The overall complication rate in the series was 6% (2/40).

DISCUSSION

In the past many surgical techniques have been employed in the repair of distal hypospadias, yet very few have stood the test of time.[3,4] If one is to attempt surgical correction of a problem that is very close to normal, then clearly one must employ a technique that provides excellent cosmetic and functional results as well as very little patient morbidity. We have been impressed with the MAGPI procedure as a method of correcting distal hypospadias that fulfills this criteria. We have been pleased with both patient and parental acceptance of the procedure, and with the feasibility of doing hypospadias repair on an outpatient basis, which the MAGPI affords.

Outpatient surgery has been well accepted for many pediatric surgical procedures. It is ideal for the children of working parents, as well as being helpful in conserving inpatient hospital beds. We have found the outpatient hypospadias repair to be cost-effective as well. Although the cost of the outpatient surgical procedure is comparable to other methods, most hypospadias procedures done on a standard inpatient basis require between seven and ten days of hospitalization with an average daily hospital cost of $300 to $500 per day. The MAGPI procedure done on an outpatient basis generates a one-day hospital bed charge with very little supplementary cost. Extended hospital stay is necessary for more proximal forms of hypospadias with more extensive types of repair; however, we have found a large number of children with distal hypospadias to be good candidates for outpatient MAGPI procedures.

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Plasma magnesium and anticonvulsant therapy

RAMZY YASSA, MD, GEORGE SCHWARTZ, MSc

ABSTRACT **Serum magnesium of 24 epileptic patients was compared to that of 24 nonepileptic patients. There was no difference in the mean serum levels of both groups whether or not the patients were receiving concomitant neuroleptic medication.**

(NY State J Med 1984; 84:114–115)

INTRODUCTION

Magnesium is an important cation in the body. It is the second most plentiful cation within the cellular fluids. Seventy-one percent of magnesium is found in combination with calcium and phosphorus in the complex salts of bone tissue.

Magnesium disturbances have been implicated in different medical, psychiatric, and as neurologic disorders.[1–3] Antiepileptic medication may cause hypomagnesemia. In a study of 223 epileptic patients chronically treated with antiepileptic medication, Christiansen et al[4] found significantly lower plasma magnesium levels in these patients compared with normal controls. On the other hand, Katz et al[5] found no significant difference in serum magnesium levels of 100 epileptic patients treated for seizures and their matched controls. Thus, the current literature is not conclusive regarding a relationship between serum magnesium levels, epilepsy, and antiepileptic medication.

We undertook a study to examine the relationship between serum magnesium levels and antiepileptic drugs in a group of institutionalized adult mentally retarded epileptic patients who were on long-term anticonvulsant therapy.

PATIENTS AND METHODS

Experimental population. All the inpatient mentally retarded population in the Adult Services of Douglas Hospital during the year 1982 were included in the study. They consisted of 48 patients, 24 epileptic and 24 nonepileptic. Of the 24 epileptic patients, 15 were men and nine women. Of the nonepileptic population, 16 patients were men and eight women. Excluded were patients with a concomitant diagnosis of schizophrenia, manic-depressive illness, and alcohol abuse. Also excluded were patients with recent myocardial infarction or physical illnesses including liver disease, diabetes, or renal impairment.

The mean age of the epileptic group was 48 years (range 25 to 77) and that of the nonepileptic population was 53 years (range 27 to 69). The mean duration of continuous hospitalization of epileptic patients was 19 years (range 2 to 55) while for the nonepileptic population it was 21 years (range 2 to 45). The mean duration of antiepileptic medication was 24 years (range 10 to 30).

Grand mal epilepsy was the diagnosis in 23 patients. One patient had temporal lobe epilepsy. All the epileptic patients except two were treated with diphenylhydantoin, with a dosage range of 200 to 400 mg per day (mean 286). Sixteen patients were also receiving phenobarbital in a dosage range of 48 to 400 mg per day (mean 161). Three patients received carbamazepine in a daily dosage of 600 mg per day.

Eleven epileptic patients received no concurrent neuroleptic medication. Thirteen others received various neuroleptic drugs, with a chlorpromazine equivalence[6] ranging from 80 to 3,000 mg per day (mean 745). In the nonepileptic patients, six received no neuroleptic drugs while 18 received neuroleptic medication, with a daily chlorpromazine equivalence of dosage varying from 50 to 1,400 mg (mean 569).

Experimental method. A personal data sheet including the name, age, sex, diagnosis, duration of current hospitalization, and current medication was completed for each patient. Blood was drawn from each patient in the morning prior to intake of any medication. Plasma magnesium was analyzed for each of the patients in the study using the Pierce Magnesium Rapid Stat Kit (Pierce Chemical Co, Rockford, IL 61105), with an Abbott 100 biochromatic analyzer. The normal values of this test in our laboratory are 1.5 to 2.1 mEq/L. Permission was obtained from the patients for taking blood samples.

RESULTS

The results are summarized in the table. All means are well within one standard deviation of each other and, given the small number of patients in each group, no difference is significant. The most notable difference represents only a 5% decrease of phenothiazine-treated epileptic patients from the nontreated nonepileptic group mean. This observed difference has the upper limit of its 90% confidence interval at 12.6%. Therefore, it is unlikely that we missed a true difference with a magnitude of 15% or more.

DISCUSSION

Our study indicates that serum magnesium levels in epileptic mentally retarded patients do not differ from nonepileptic mentally retarded patients. Even when neuroleptic medication was added to antiepileptic medication, we found no significant differences between patient groups. Our results confirm those of Katz et al[5] and Herpiertz et al[7] who found that serum magnesium levels were not significantly different in epileptic patients and in nonepileptic controls. These findings are, however, in contradistinction to those of Christiansen et al[4] and Chhaparwal et al[8] who found a decrease in serum magnesium levels in epileptic patients when compared to controls.

Mean Magnesium Levels in the Patient Population

Patients	No.	Mean, mEq/L	SD	Range, mEq/L
With epilepsy				
Total	24	1.77	0.18	1.5-2.1
With phenothiazines	13	1.74	0.16	1.5-2.0
Without phenothiazines	11	1.79	0.15	1.5-2.1
Without epilepsy				
Total	24	1.78	0.15	1.5-2.0
With phenothiazines	18	1.76	0.15	1.5-2.0
Without phenothiazines	6	1.83	0.16	1.6-2.0

From the Psychiatry Department, Douglas Hospital Centre, Verdun, Quebec, Canada.

Address correspondence to Dr Yassa, Psychiatrist, Douglas Hospital, 6875 Lasalle Blvd, Verdun, PQ H4H 1R3, Canada.

In conclusion, our study of epileptic and nonepileptic mentally retarded patients showed no effect of antiepileptic medication on serum magnesium levels. The same results were noted in patients with and without neuroleptic medication whether or not antiepileptic medication was added to the treatment regimen.

Acknowledgment. The authors wish to thank Nicole Daoust for her secretarial help.

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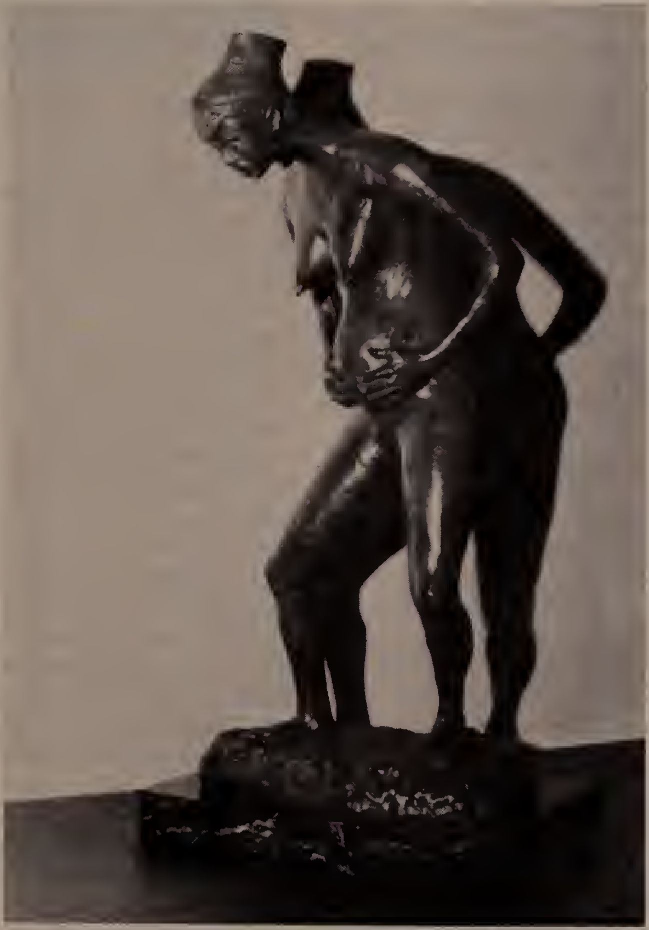
PAUSE



A NEW LIFE IN AFRICA

I will probably never again have the opportunity of witnessing so primitive a delivery as the one that took place one hot afternoon during the time when I was on a WMA medical project near the Libyan-Chad border.

This bronze, which I completed a year later, depicts the young woman as she was beginning to experience her first labor pains. It was her sheer grace and beauty while she was still standing that I hoped to be able to capture. Moments later, assisted by the two old women who were accompanying her, she was lowered to a squatting position against the base of a tree, and it was there that she gave birth.

More amazing was that within the hour she and the newborn infant were up and on their way back to their village.

STEPHEN NORDLICHT, MD

Cerebral vascular occlusion followed by renal failure in a 62-year-old woman

CASE PRESENTATION

Robert Moskowitz, MD (Resident Physician): A 62-year-old woman developed left-sided weakness and fell to the ground while arising from a chair. There was no loss of consciousness, seizure activity, or incontinence. For the preceding two weeks she had been noted to be somnolent, confused at times, and irritable.

Four years previously she had developed a left hemiparesis, with resolution and return of good function; thereafter she was treated with dipyridamole (Persantin). For several years, her hypertension had been treated with triamterene, hydrochlorthiazide, and metoprolol. She was said to have had hypothyroidism and was taking levothyroxine sodium (Synthroid) 50 μg daily.

Physical examination on admission revealed no acute distress. The blood pressure was 180/90 mm Hg; the pulse rate was 64 and regular; the respiratory rate, 22 per minute; and the temperature, 37.7°C (100°F). The general examination revealed a silastic lens implant in the left eye; there were normal carotid pulsations without bruits. Results of cardiac examination were negative. Neurologic examination revealed a left homonymous hemianopsia, a left central facial weakness, a left hemiparesis with weakness greater in the upper than in the lower extremity, and bilateral extensor plantar responses. The left deep tendon reflexes were slightly more brisk than those on the right. Her mental status seemed normal, although with intermittent confusion. No sensory defects could be detected.

Results of urinalysis were normal. The hemoglobin was 14.8 g/dL; the hematocrit 43%; the red blood cell indices were normal. The WBC count was 7,300/mm^3, with a normal differential count. The values for serum sodium, potassium, chloride, bicarbonate, glucose and BUN were within the normal range. The electrocardiogram showed a sinus bradycardia with a first-degree AV block. The chest x-ray and echocardiogram showed no abnormalities.

The x-rays and computerized tomograms will be discussed by Dr Stern.

The electroencephalogram was consistent with a right hemispheric dysfunction and a right structural lesion.

A myocardial infarction was ruled out with the aid of serial EKGs and serial enzyme studies. A 24-hour Holter monitor study showed only sinus rhythm with infrequent premature atrial and ventricular contractions.

Heparin therapy was initiated; the patient's neurologic deficit improved. One week after admission, a right carotid angiogram via a femoral artery entry showed nearly complete occlusion of the middle cerebral artery at its trifurcation; there was no evidence of collateral circulation or of vascular disease of the carotid system. At the end of the procedure, cyanosis of the soles of the feet and of the great toes was noted. Bilateral peripheral arteriogram revealed marked plaque disease from the aortic bifurcation downward, with bilateral occlusion at the level of the popliteal arteries. Bilateral antegrade entries into the femoral arteries permitted the injection of streptokinase 5,000 units/hour via each catheter, with return of palpability of the popliteal arteries and improved capillary filling. A sonogram of the abdomen was reported to be negative for evidence of aortic aneurysm. Several hours thereafter, the pulses below the femoral arteries disappeared, and the legs assumed a mottled appearance.

The following morning, the patient became tachypneic, tachycardic, hypotensive, and febrile. The central venous pressure was found to be 4 cm; a Swan-Ganz catheter revealed a pulmonary capillary wedge pressure of zero, right atrial pressure of zero, and right ventricular systolic/diastolic pressures of 11/0.

Over the next 24 hours, the patient received 5.1 L of fluid; the urine output decreased to 220 mL despite the fluid challenge and the use of loop diuretics. The serum sodium was 124 mEq/L, potassium 4.4 mEq/L, and the serum osmolality 298 mosm. The urine sodium was 54 mEq/L, potassium 36 mEq/L, and osmolality 342. The serum creatinine was 2.0 mg/dL, and the BUN 37 mg/dL; the lactic dehydrogenase (LDH) was 346 IU/mL (normal up to 225 IU/mL). The hematocrit was unchanged at 43%; the WBC count rose to 20,000/mm^3 with a left shift.

The patient's neurologic status progressively deteriorated; she responded to verbal and noxious stimuli with purposeless movements. Two days after the angiogram, the serum creatinine level had risen to 4.3 mg/dL, the BUN to 58 mg/dL, the LDH to 1,085 IU/mL, the WBC count was now 6,100/mm^3, the platelet count 105,000/mm^3. Cerebral function continued to deteriorate and the patient lapsed into unconsciousness; the blood pressure remained elevated at 220/110 mm Hg. On that same day, she developed ventricular tachycardia, followed by asystole and cardiac arrest from which she could not be resuscitated.

Harvey Stern, MD (Associate Director of Radiology): The initial CT scan of the head showed an area of decreased attenuation in the right frontoparietal area, of either recent or remote origin, without significant mass effect and no

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Based on the clinicopathologic conference (CPC) held at Maimonides Medical Center, Brooklyn, NY, on June 13, 1983.

Moderator: David Grob, MD, Director of Internal Medicine; *Clinical Discussion:* Edward Arsura, MD, Assistant Director of Internal Medicine; *Pathology Presentation:* Stanley Minkowitz, MD, Director of Pathology.

Editor: JOHN T. FLYNN, MD.

Address correspondence to Dr Flynn, Consulting Editor, *New York State Journal of Medicine*, PO Box 5404, 420 Lakeville Rd, Lake Success, NY 11042.

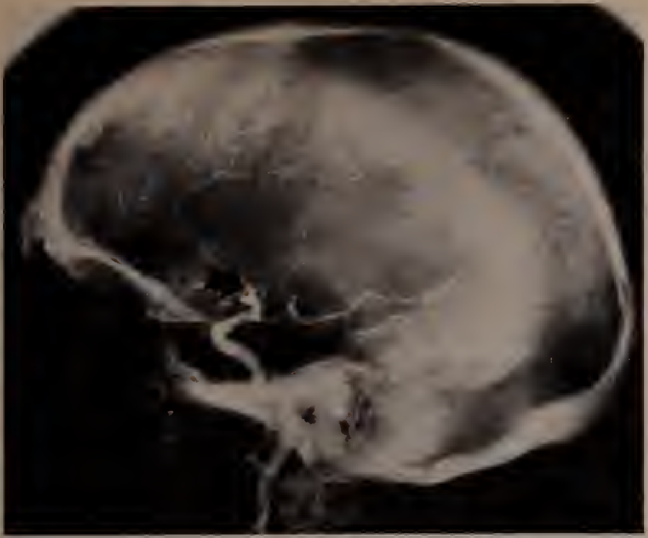

FIGURE 1. Complete occlusion of right middle cerebral artery at trifurcation of internal carotid artery (arrow).

evidence of calcification or bleeding. Without evidence of intracranial bleeding, it was reasonable to postpone angiographic delineation of the cerebral vascular lesion for several days at least. A mild degree of cerebral atrophy was present.

Her progressive deterioration and the clinician's concern about intracranial bleeding while the patient was receiving heparin probably were the indications for a repeat study. Repeat CT study revealed the same findings, without evidence of blood in the ventricles or subarachnoid hemorrhage. There was no significant edema, shift of the ventricles, nor enhancement with administration of contrast medium.

During angiography, the intra-arterial catheter was placed without difficulty, with the tip below the right common carotid bifurcation. The initial injection revealed a normal main carotid system, a normal anterior cerebral artery, and a complete occlusion at the trifurcation of the middle cerebral artery (Fig 1). The remaining cerebral and extracerebral branches of the right common carotid artery appeared normal, with no plaque formation or narrowing.

When the procedure was completed, the neuroradiologist noted mottling of the lower extremities. He requested the angiographer to perform a peripheral study, during which the usual one injection of contrast dye demonstrated extensive atheromatous disease in the aorta below the level of L-3, in the common iliacs and in their major branches. We were not aware of any reason to study the more proximal aorta. The superficial femoral branches, although atheromatous, were patent; but their popliteal trifurcations were completely occluded bilaterally, with abrupt tapering and no collateral flow (Fig 2). The delayed films demonstrated no run-off and no filling of the major branches of the popliteal arteries on either side. All of these findings are consistent with the diagnosis of arterial embolism; the presence of collaterals, on the other hand, would have suggested arterial thrombosis in situ, superimposed on atheromatous disease.

The chest roentgenogram on admission was unremarkable, except for borderline heart size; there were no pulmonary infiltrations or effusions.

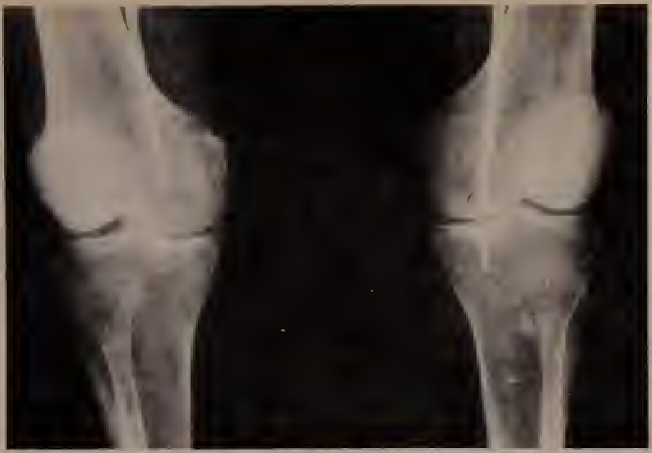

FIGURE 2. Embolic occlusions at trifurcations of both popliteal arteries, with abrupt tapering and no collateral flow.

Aaron Bick, MD (Resident Physician): Dr Stern, do you think that the occlusions in the lower extremities were related to the angiographic procedure?

Dr Stern: There is a recognized incidence of embolization anytime the aorta is catheterized. The incidence is small, particularly in patients who are on anticoagulant therapy. In this patient, it is certainly a possibility. In order to minimize the likelihood of complications during the procedure, we maintain a constant heparin infusion. This would not affect the thrombi already present, but the incidence of procedure-related events is said to be lower in patients who have been on long-term heparin therapy. We have not had problems with such patients.

David Grob, MD (Director, Department of Internal Medicine): Could these thrombi in the popliteal arteries result from atherosclerotic emboli initiated by insertion of the catheter into the aorta?

Dr Stern: That is always a possibility. However, there is a significant though very low incidence of embolism associated with this catheterization procedure, irrespective of whether atheromatous disease is present in the aorta or not. This complication is not clearly understood, but our use of heparin is an effort to prevent the occurrence of embolism. Another problem is mechanical break-off of plaques, which of course would not be affected by heparin.

The incidence of atherosclerotic embolism associated with catheter study of the carotid and cerebral circulation is reported to be less than 0.5%; the incidence in our hands has been even lower. I cannot recall the last such case here; in the last five to six years we have performed about 500 catheterizations per year.

Dr Grob: The morbidity related to this procedure, encompassing all untoward events, is less than 1%; and the mortality is under 0.1%.

Dr Stern: Over many years, we have had no mortality that we could relate to these procedures.

J. Hyman, MD (Resident Physician): This lady might have been a perfect candidate for subtraction flow studies, because of her hypertension and her previous occlusive vascular events.

Dr Stern: I agree. Gross lesions such as carotid occlusions are easily detectable with this technique. It would have been used, if this patient had been in sufficiently good condition to be temporarily transferred to another institution where the technique is available.

CLINICAL DISCUSSION

Edward Arsura, MD (Assistant Director of Internal Medicine): There were three major processes in this patient's illness: the first was the cerebral vascular accident two weeks before her final admission; second, the peripheral embolic phenomena; and third, the anuria, followed by a progressive downhill course.

In contrast to the usual sudden onset of a so-called "routine" stroke, this patient presented prodromes of confusion, irritability, and intermittent somnolence, which would not be entirely compatible with one embolic or occlusive event in the carotid or cerebral arteries. Possibilities deserving consideration in the differential diagnosis include hypertension with secondary congestive heart failure or renal insufficiency, undertreated hypothyroidism, and metabolic abnormalities. Hypertensive encephalopathy would not seem likely with a blood pressure of 180/100 mm Hg in a previously hypertensive patient.

On admission, the patient presented with bilateral homonymous hemianopsia and weakness, compatible with damage to the non-dominant hemisphere. Her confusional state might have obscured any sensory deficits. On clinical grounds, this lady was diagnosed correctly as having a middle cerebral artery (MCA) occlusion, and the CT scan supported this impression. Many foci of decreased attenuation in the distribution of the MCA often signifies a large embolus to a major cerebral artery, with dissolution of the embolus and dissemination of the fragments to distal branches.

Embolism is the most common single cause of cerebral vascular accidents, occurring in about one third of cases. Clues to the diagnosis of embolism are the very abrupt onset of symptoms, the presence of possible sources of emboli such as diseased cardiac valves or prosthetic valves, the findings of concurrent renal or splenic infarction, the visualization of retinal emboli, the occurrence of cerebral vascular occlusion in younger patients, the lack of prodromal transient ischemic attacks, and the absence of atherosclerosis elsewhere. Radiographic evidence of concurrent occlusions of more than one artery also is suggestive of embolism.

The echocardiogram did not indicate an intracardiac source of emboli. There is no indication of an occult mitral or aortic stenosis, nor of any chronic illness likely to produce marantic endocarditis. Blood cultures of course were in order, to rule out bacterial endocarditis. The electrocardiogram demonstrated a prolonged PR interval with sinus bradycardia, which, if not secondary to the use of beta-blocking medications, might suggest a sick sinus syndrome, with its increased incidence of thromboembolic events. This diagnosis was unsupported by the Holter monitor study, which showed only sporadic premature contractions. Atrial fibrillation, with its high incidence of embolic phenomena, was not present. The patient had none of the classical symptoms nor physical and echocardiographic findings of atrial myxoma or cardiomyopathy. Myocardial infarction, with its tendency to promote intracardiac mural thrombi, was ruled out by serial EKGs and enzyme studies. Her normal arterial oxygen saturation would practically exclude the possibility of paradoxical embolism via an atrial or ventricular septal defect.

The history does not reveal a clinical situation commonly associated with air or fat embolism. However, cholesterol emboli are commonly associated with preceding neurologic symptoms, suggestive in some instances of diffuse cerebral disease.

Evidence of bruits in the great vessels, preceding transient ischemic attacks of short duration (less than 15 minutes), retinal emboli, the presence of extracranial collateral circulation, coexistent atherosclerosis in other organs, and onset during sleep are all indicative, though not sensitive, for cerebral thrombosis. A minority of 15% to 20% of patients in whom cerebral thrombosis has occurred, will present a pattern of so-called "stuttering" cerebral infarction over a 24- to 48-hour period, which is fairly specific for thrombosis.

In this patient, there is little to support the possibility of nonatherosclerotic obstructive vascular disease, such as polyarteritis nodosa. Collagen vascular diseases, presenting initially with an isolated central nervous system deficit, would be most unusual. There was no history of trauma, and no evidence of a spontaneous dissection of the aorta. Fibromuscular dysplasia of arteries should have been evident on the arteriogram.

A cerebral lacunar infarct ordinarily would have produced corticospinal tract weakness with equal involvement of the upper and lower extremities; on the contrary, this patient's upper extremity was affected more than the lower extremity. Her abnormal electroencephalogram, reflecting a cortical lesion, would not be expected with lacunar infarction, which is usually located deeper beneath the cortex. A much more limited defect would be expected with a lacunar infarct.

Of all the forms of cerebral vascular accidents, the most readily diagnosed on a clinical basis are hypertensive hemorrhage, subarachnoid hemorrhage, and arteriovenous aneurysm—none of which appear likely in our patient, nor were they supported by the diagnostic studies performed. On heparin therapy, she did fairly well. The early use of heparin would not resolve the initial clinical events, but was intended to prevent their recurrence. The use of heparin is reasonable therapy if embolism is diagnosed.

The second important aspect of her clinical course is related to the events that followed the angiographic procedure and that were described by Dr Stern. The overwhelming majority of emboli to both upper and lower extremities originate in the heart, although a small percentage to the latter originate in the aorta. The heart must be ruled out initially, whenever possible, as the source of embolism. Embolic phenomena without any preceding catheterization could have been compatible with spontaneous atheroembolism, originating in the aorta. Rarely popliteal aneurysms can seed the more peripheral arteries with emboli, but we see no evidence of such aneurysms here.

Streptokinase therapy intended for dissolution of thromboemboli seemed not to affect the mottling of the lower extremities, which worsened over the remaining days of the patient's life. Mottling of extremities and toes in a fishnet pattern (livedo reticularis) is due to occlusion of vessels 50 to 600 microns in diameter. The occluding particles are probably not thrombi; therefore, we would not expect them to be influenced by the streptokinase therapy.

Urinalyses would have been mandatory in the search for multiple emboli, as would fundoscopic examination of her good eye, in the search for cholesterol emboli and plaques dislodged by the catheter.

The third important aspect of this patient's disease process was the subsequent development of renal failure. Oliguria and complete anuria marked her terminal course, in spite of very adequate fluid replacement and good maintainence of blood pressure. Acute onset of renal insufficiency with anuria can occur with urinary tract obstruction, but there was no clinical suggestion of that in this case. One cause of urinary tract obstruction, although not likely in my judgment, could be a retroperitoneal hematoma secondary to heparin, with bilateral compression of the ureters. If present, a retroperitoneal hematoma most likely would have been identified during the ultrasound examination of the abdominal aorta. In ruling out obstruction, keep in mind that the abdominal films after the injection of contrast dye showed excretion from both kidneys, even though with only faint visualization.

With regard to other possible renal or prerenal causes of acute renal insufficiency, the patient was initially dehydrated, but this was promptly resolved with the administration of fluids. The urinary electrolyte levels point toward a renal cause of oliguria and anuria, as did the urine osmolality. The urinary sodium excretion was fairly high; the calculated percent fractional excretion of sodium greater than 1 would support the idea that the cause of the anuria was primarily renal.

The patient received furosemide 140 mg together with fluid administration shortly after the onset of renal insufficiency, in an attempt to convert oliguria to non-oliguric renal failure. Earlier, she had been given radio-contrast dye which may be nephrotoxic and which at times may lead to acute tubular necrosis. In 50% of patients with acute tubular necrosis after dye injection, a flat plate of the abdomen obtained 24 hours after the procedure will still permit visualization of the kidneys. This however can be found in acute tubular necrosis due to other causes. Some patients with prior renal insufficiency will develop acute tubular necrosis following nephrotoxic dye injection; however, most such patients are diabetic with preexisting renal impairment.

Following massive emboli to the lower extremities, one should consider extensive skeletal muscle damage, rhabdomyolysis, and myoglobinuria leading to renal insufficiency. The urine should have been checked for the latter; and serial serum creatinine phosphokinase determinations late in her course would have been helpful. However, this patient did not have the other components of myoglobinuric renal failure, such as an elevated serum potassium, serum phosphate, or serum calcium value. Extensive cellular tissue destruction can lead to urate nephropathy; here, one should determine uric acid-to-creatinine ratio in the urine.

There is no indication of an allergic interstitial nephritis; the patient was taking no medications known to cause that condition.

Progression to anuria in this patient is very significant. Once urinary tract obstruction is excluded, we are left with few causal entities, mostly involving renal arterial damage—bilateral renal artery emboli, bilateral renal thrombi, and bilateral renal artery dissection. Severe malignant hypertension and severe acute glomerulonephritis are conditions from which this patient obviously did not suffer. She in no way resembles the typical septic hypotensive patient with intrapartum or postpartum complications who presents with bilateral renal cortical necrosis.

Atheroemboli can be large and can occlude large vessels; cholesterol emboli tend to be much finer and therefore to occlude much smaller vessels. Large pieces of thrombus may be dislodged, and in the process cholesterol deposits may enter the blood stream; both may affect the kidneys.[1] Aortic aneurysm repair and renal angiographic procedures have been associated with cholesterol embolism, with the development of livedo reticularis and progressive renal failure.[2,3] In 1961 Feder from this hospital described the "purple toes" syndrome which he attributed to a vasculitis secondary to warfarin sodium therapy. Other authors suggested that this group of patients had sustained atheroemboli and that the anticoagulant was preventing the formation of a thrombotic covering over the sites of origin of cholesterol emboli. After a diagnosis of cholesterol embolism is established, anticoagulant therapy is probably contraindicated. If a diagnosis of atheroembolism could have been made in this patient, heparin would not have been used, although I don't think such therapy had any effect on the eventual outcome.

Patients with atheroemboli to the kidneys commonly have hypertension after renal artery occlusion, with a progressive rise in the blood pressure that remains elevated even in the terminal stages, as seen in this patient.[4] The pancreas and the mesenteric arteries are also frequently involved. Probably the best method by which to make the diagnosis is a biopsy of muscle from an involved extremity which, if positive, would show cholesterol deposits.[5] When this disease occurs spontaneously, 10% of patients will present with prominent myalgias, elevated sedimentation rates, eosinophilia, fever, and livedo reticularis.[6] The condition can be confused with polyarteritis nodosa and with polymyalgia rheumatica; the latter however is not so destructive a disease. On clinical grounds, the differentiation however is very difficult to make.

Thus, we have a lady who appeared to be fairly healthy up to about three weeks prior to admission, who presented with multiple vascular occlusive phenomena, most probably emboli involving the kidneys, extremities, and central nervous system; with no evident cardiac source of emboli. We are left with a disease of small vessels related to multiple atheroemboli.

Dr Grob: Was a lumbar puncture done?

Dr Moskowitz: No.

Dr Grob: Every patient who is admitted with a so-called stroke ought to have an examination of the spinal fluid, at an appropriate point in the diagnostic work-up. Embolic occlusion of the middle cerebral artery and thrombotic occlusion as well, can produce red blood cells in the spinal fluid, originating from areas of hemorrhagic infarction of the brain. Controlled studies have shown that early heparinization of such patients is associated with an increased mortality. In the case of embolic occlusion, of course, one wishes to prevent a recurrence and therefore would anticoagulate shortly after the acute event. In bacterial endocarditis with embolism from an infected valve, anticoagulants are not used because a mycotic infected aneurysm of an artery is more likely to rupture in those circumstances. However, I doubt that the immediate heparinization in any way affected the final outcome in this particular patient.

I would like Dr Lipner to comment on the patient's terminal anuria.

H. Lipner, MD (Director of Nephrology): Most instances of thromboembolic disease involving the kidneys initially will be unilateral and therefore will present with generally mild initial symptoms, such as fever, hematuria, and little if any impairment in renal function. At this stage, we discover the condition only incidentally during the course of a renal work-up, with evidence of reduced function of a portion of one kidney. Treatment with heparin is often followed by resolution of the problem. In other cases, the patient has presented with indications of embolic disease to one kidney, and during subsequent followup becomes anuric, due to recurrent embolism. Anuria close to the onset of this condition would ordinarily imply massive embolism from the lower aorta including saddle emboli, atherosclerosis of extensive areas of the aorta, and aneurysms. Of course, embolism to a solitary kidney would precipitate anuria early in the clinical course.

This patient underwent catheterization of the aorta and conceivably plaques could have broken off and embolized to both kidneys. But even here the catheter was not directed to the orifices of the renal arteries; and during the procedure the kidneys were visualized by the excretion of dye. So I doubt that there was complete occlusion of both renal vessels consequent to the procedure. More likely, atheromatous emboli occurred to small branch arteries.

In the presence of normal kidneys, the incidence of renal failure with such procedures using contrast dye injections is well below 1%; however, with chronic renal insufficiency, worsening occurs in about 30% of patients. So if the patient has embolic disease that involved the trifurcation of the popliteal artery as well as the renal arteries, and in addition if she underwent a procedure using dye, it is possible that a partial renal dysfunction progressed to acute anuria.

Acute tubular necrosis by itself rarely produces anuria, but the addition of contrast dye can readily convert acute tubular necrosis without anuria to an anuria state.

The point about the rise of arterial blood pressure with embolic renal artery stenosis is a good one, and we very often see that.

Dr Grob: There was no evidence of a cerebral tumor, although we have on occasion mistaken a cerebral infarct for a tumor, and vice versa.

Dr Arsura: The initial symptoms during the several weeks prior to admission might suggest an intracranial tumor; the subsequent events during her hospital admission, much less so.

Dr Bick: Do you think the rise in LDH and in serum bilirubin was due to the streptokinase therapy?

Dr Arsura: These might be related to renal infarction and to severe ischemia of other organ-systems.

CLINICAL DIAGNOSES

Idiopathic spontaneous atheroembolism from the aorta, most likely from the arch, initially involving the carotid artery and its branches.

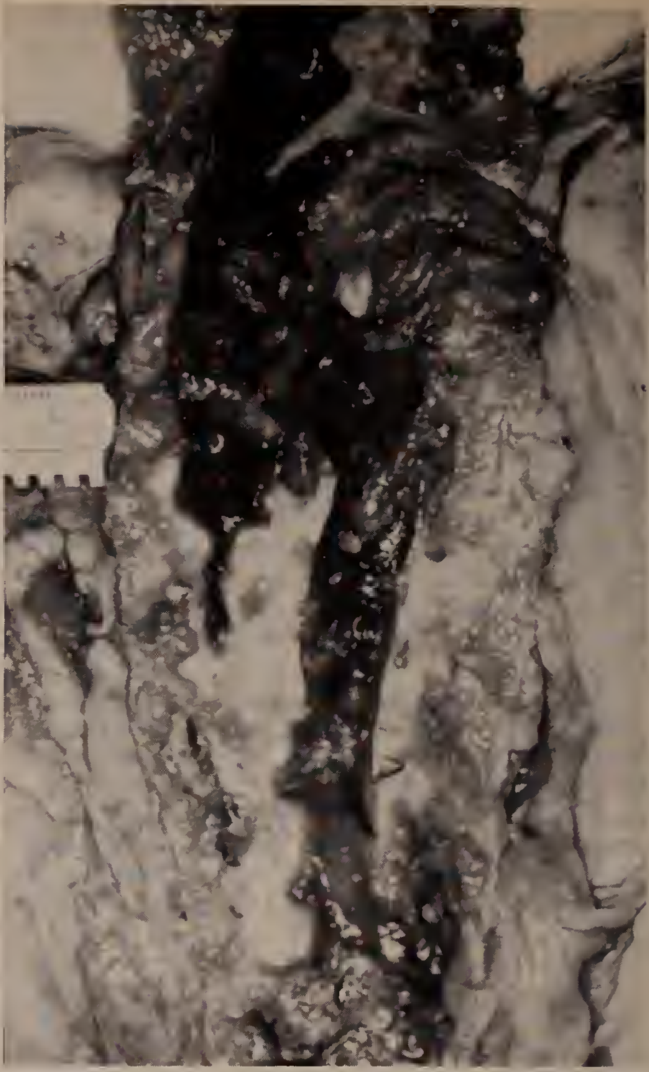

FIGURE 3. Severe atherosclerosis of abdominal aorta, with extensive luminal thrombosis.

Embolization from the aorta to the renal and extremity vessels, possibly secondary to the intravascular catheterization.

PATHOLOGY PRESENTATION

Stanley Minkowitz, MD (Director of Pathology): On gross examination, there was severe atherosclerosis of the aorta, together with extensive thrombosis along much of the abdominal aorta (Fig 3). No doubt the arterial catheter had been passed through areas of aortic mural thrombus and in all probability dislodged some of the thrombus material. No doubt the clinical picture resulted from a combination of thromboembolism and cholesterol embolism.

The thoracic aorta contained grayish tissue representing mural thrombus, together with masses of cholesterol and postmortem clot. Thus the entire aorta was covered spottily with mural thrombi. The reason for the impressive atherosclerosis in this patient remains obscure.

Sections through the calcific atherosclerotic plaques revealed the usual needle-like negative images or clefts that represent the areas from which the cholesterol crystals and

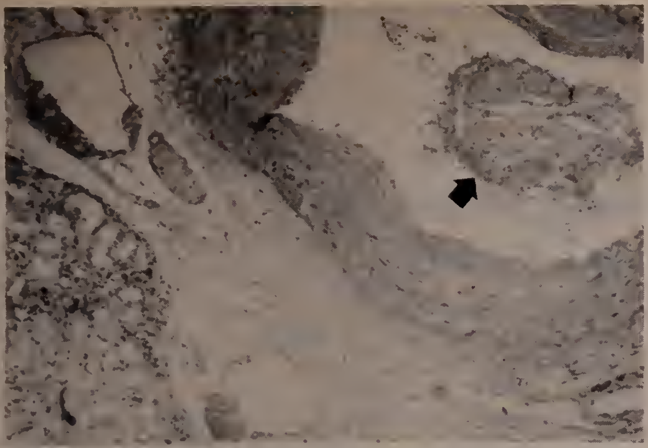

FIGURE 4. Cholesterol embolus to tertiary renal artery demonstrates cholesterol clefts (arrow).

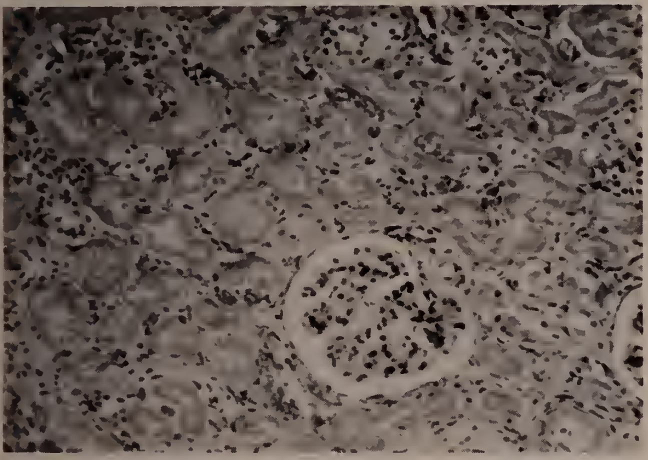

FIGURE 5. Acute renal tubular necrosis, with loss of cellular nuclei.

masses were dissolved out in the preparation of the slide. Even the mural thrombi showed similar cholesterol clefts. Some areas of mural thrombosis were of recent origin, probably no more than a few hours old.

The major renal arteries were fully patent. In the tertiary interlobulary branches of the renal arteries, we found cholesterol emboli, and emboli originating from the aortic thrombi (Fig 4), though numerically insufficient to cause renal failure. More likely the cause of the renal failure was the combination of the emboli and the contrast dye, since this patient also had clear evidence on microscopic examination of acute tubular necrosis. The affected tubules contained cells without nuclei, a finding not related to postmortem autolysis (Fig 5). There is no evidence of glomerulonephritis. The arterioles showed a significant arteriolonephrosclerosis that could account for the hypertension. The kidney findings are consistent with the effects of catheterization followed by acute tubular necrosis, with emboli showing cholesterol clefts.

The spleen showed evidence of cholesterol emboli of an older vintage, since they were fully organized and adherent to the vessel wall. They were at least a month old but could have been present for years (Fig 6).

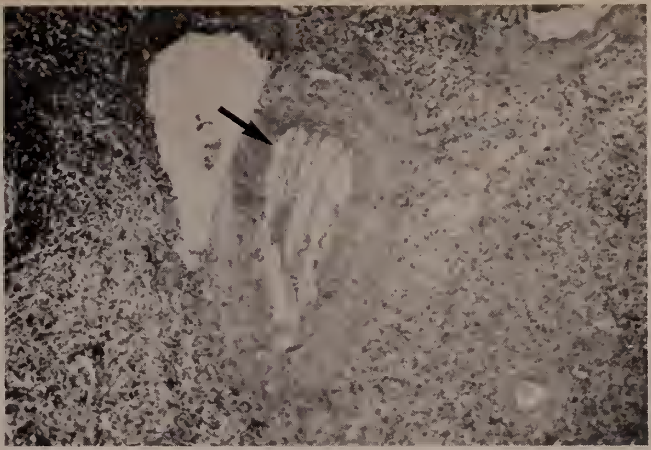

FIGURE 6. Cholesterol embolus, old, in branch of splenic artery, demonstrates cholesterol clefts (arrow).

The small bowel showed some autolysis but also recent thromboembolism in the submucosal area, probably as a result of dislodgement of mural thrombi from the aorta.

The middle cerebral artery contained a thromboembolus, without cholesterol however. There was encephalomalacia, but curiously enough, she also had a marked accumulation of polymorphonuclear cells that would be unusual in a straightforward arterial thrombus and that raised the question of a septic embolus, the source of which we could not find. The other possibility would be a secondarily infected infarct of the brain, which seems most likely to me. In effect, the patient had a vascular occlusion, and then developed a focal meningoencephalitis.

FINAL ANATOMIC DIAGNOSES

1. Severe calcific ulcerated atherosclerotic cardiovascular disease, mainly involving the abdominal aorta and arch of aorta.
   a. Mural thrombosis of abdominal aorta.
      Multiple thromboemboli in submucosal arteries of small and large bowel.
      Multiple cholesterol emboli in kidney, liver and spleen.
   b. Mural thrombosis of arch of aorta.
      Total occlusion by thromboemboli of middle cerebral artery.
      Acute cerebral infarction, right temporofrontal, with meningoencephalitis.
2. Status post cerebral artery angiogram (femoral approach)
   a. Tubular necrosis of kidneys.

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Compound X given intravenously

On the history of the nitrogen mustards

LEONARD G. DAUBER, MD

Alkylating agents were developed in the secret gas warfare program in both world wars. An explosion in Naples harbor and the exposure of seamen to these agents in World War II led to the observation that these particular agents caused marrow and lymphoid hypoplasia, and led to the use of these chemicals in the lymphomas.[1]

The nitrogen mustards (methyl-bis-beta chloroethylamine hydrochloride and tris-beta chloroethylamine hydrochloride), prototypes of the alkylating agents, were developed in the gas warfare programs of World Wars I and II. The use of these agents in the treatment of lymphoproliferative malignant diseases (Hodgkin's disease and the non-Hodgkin's lymphomas) was a direct outgrowth of these programs and of the careful and methodic investigations of medical scientists. The explosion in an Italian harbor during the second World War of a ship carrying mustard gas occurred a year after the introduction of these compounds into clinical medicine and therefore is an unrelated episode of military history. (See appendix)

Dichloroethyl sulfide, a combination of sulfur chloride and ethylene, was first synthesized in 1860 by an English chemist, Guthrie. Because the product had a slight acrid aroma resembling mustard oil, it was referred to as mustard gas. In 1866, Victor Meyer studied its vesicant and inflammatory properties in laboratory animals.[2]

Although some scientific studies were done in the succeeding years, dichloroethyl sulfide achieved lasting notoriety only because of its use as an agent of chemical warfare in World War I. The origins of chemical warfare have been described in detail by Trumpener.[3] Despite the Hague Conference of 1899 in which the signatories agreed not to "employ poison or poisoned weapons" or the "use of projectiles the sole object of which is the diffusion of asphyxiating or deleterious gases," both the French and Germans had developed and put into use gas-diffusing projectiles (cartouches and grenades suffocantes, and T-shells containing xylyl bromide which transformed into an irritant vapor). These went virtually unnoticed by the forces at whom the artillery fire was directed. However, in April 1915, at Ypres, "an escalation of combat technique" was essayed.[3]

The Germans planned the use of cloud-gas dispersion of chlorine gas, a much more noxious vapor than previously used sternutatory and irritant substances. The entrenched battle positions at Ypres in which the Germans opposed French and Canadians along a wide arc seemed the perfect site for a trial use of this toxic gas, the purpose of which would be to dislodge enemy troops from their fixed positions; World War I had devolved to these entrenched battle lines. The prevailing tactics of the general staffs of all the fighting armies required artillery bombardment followed by frontal assault. High casualty rates were not a deterrent since the army with the superior gunnery and numbers of troops would prevail. This war of attrition was ripe for new techniques to obviate the carnage between the trenches, and cloud-gas dispersal offered the German High Command a tactical advantage. Prevailing winds had to be suitable and the concentration of storage cylinders installed and protected. Preparations along the German lines were completed by mid-April 1915, with only little difficulty and without counterpreparations by the Allies. On the afternoon of April 22, 1915:

> At five o'clock a fearful din of guns broke out and heavy shells struck with a reverberating crash on Ypres and many villages rarely or never touched before. And to the nostrils of the men nearer the front came the smell of devilish incense. Those nearer still to the trenches north of Ypres saw two curious wraiths of greenish-yellow fog creep forward, change to a blue-white mist. It hung, as it had come, over the front of the two French divisions, one Algerian, one Territorial, which joined up with the British and held the left of the salient. Soon, officers behind the British front . . . were startled to see a torrent of terrified humanity pouring backward . . . coughing and pointing to their throats as they fled.
>
> The fugitives left behind them a gap in the front four miles wide, filled only by the dead and by those who lay suffocating in agony from chlorine gas poisoning.[4]

By 1917, other agents, more effective and more virulent than chlorine (as phosgene, lewisite), had been put into use by both combatant sides, culminating in the introduction of sulfur mustard (dichloroethyl sulfide) gas at Ypres, in a series of extended battles, named Passchendaele, after a nearby village.

The United States Chemical Warfare Service undertook the examination of dichloroethyl sulfide at its Ann Arbor affiliated laboratories. Such investigations were predicated on the observations that "mustard gas was persistent; it [had] proved to be a high casualty producer, and it [had] considerably widened the scope of chemical warfare."[5]

Address correspondence to Dr Dauber, 1180 Morris Park Ave, Bronx, NY 10461.

Various samples, including those obtained from captured German yellow-cross and green-cross shells, were studied. The conclusions were: "Mustard gas is essentially a local poison exerting its action directly upon those tissues with which it comes in contact. The very mildest concentrations usually affect the eyes first, then the skin and respiratory tract."[2]

But systemic effects of dichloroethyl sulfide were also noted. Severely gassed cases, after an initial leukocytosis, developed a marked leukopenia. Small intravenous doses in laboratory animals (rabbits) brought about a profound leukopenia with destruction of granulocytes in the bone marrow; similar changes were noted in the bone marrow of human cases.[6]

This specific poisoning of the hematopoietic system went unnoticed in the medical community. The vesicant and inflammatory effects prompted Adair and Bagg in 1931[7] to use dichloroethyl sulfide to hinder the appearance of tar-induced tumors in rat skin, and to apply it topically in the treatment of a few patients with skin cancers (epitheliomas, melanomas, and penile cancer.)

With World War II, a systematic review of this compound and related agents was undertaken under secret government contracts. At Yale University, Major Alfred Gilman (from the Edgewood Arsenal) and Dr Louis S. Goodman were working with nitrogen (substituted for sulfur) chloroethyl amines.

> A familiar scene at Yale early in 1942 was Phillips timing the kinetics of cyclization [of the beta-chloroethyl amines to form the highly reactive ethylene immonium ring] and Goodman and Gilman with a battery of syringes and a hoard of rabbits prepared to inject the reaction product at the appropriate time. The jibes of our colleagues that the enemy did not intend to attack with hypodermic needles were ignored.[8]

According to Gilman,[8] "The systemic effects of these nitrogen mustards were far more fascinating than the blisters they produced on the skin . . . . The studies in rabbits provided a daily reminder of the remarkable sensitivity of lymphoid tissue to the cytotoxic action of the nitrogen mustards . . . . The problem was fundamental and simple: could one destroy a tumor with this group of cytotoxic agents before destroying the host."

A mouse with a transplanted murine lymphoma was selected to study the susceptibility of the experimental tumor to nitrogen mustard. Instead of succumbing in three weeks as was expected, the mouse lived 84 days. The studies were extended and "were sufficiently encouraging to consider a therapeutic trial in man." Gustav E. Lindskog, MD, assistant professor of surgery at Yale, agreed to supervise the clinical trials.[8]

> To put the reader in proper perspective it is necessary to think back to the early 1940s. As a result of the impact of sulfonamides, medicine was beginning to emerge from a period of therapeutic nihilism, but new drugs were still regarded with suspicion. This was particularly true in the area of malignant disease . . . . The administration of drugs other than an analgesic in the treatment of malignant disease was the act of a charlatan. Add to this the fact that the nitrogen mustards were classified at the time as "top secret" and that the entry on the patient's chart read "0.1 mg per kg compound X given intravenously." Truly, Lindskog had great faith in his pharmacologic colleagues.[8]

The patient selected had advanced lymphosarcoma, resistant to x-ray treatment, with general glandular enlargement and a superior vena caval syndrome. "The response of the first patient was as dramatic as that of the first mouse . . . . By the fourth day of treatment obstructive signs and symptoms were relieved and by the tenth day, when the series of injections was terminated, cervical masses were no longer palpable."[8] Although the patient subsequently relapsed, additional patients were treated at Yale and elsewhere with palliative success. By the end of the war and with the lifting of secrecy requirements, Goodman et al[9] could report on their combined experience using the nitrogen mustards in the treatment of patients with Hodgkin's disease and other lymphoproliferative disorders.

By 1969, combination chemotherapy (nitrogen mustard with other agents) by DeVita et al[10] had resulted in the apparent cure of Hodgkin's disease in nearly half the responders to treatment. This marked the first use of drugs to cure a malignancy and remains the foundation of modern medical oncology.

APPENDIX

The Allied invasion of Italy had begun on September 9, 1943 with the United States Fifth Army (General Mark Clark) in amphibious landings on the beaches at Salerno. Bari, on the eastern (Adriatic) Italian coast, which had been captured by the British First Airborne Division, was to serve as the supply port for the Allied offensive to the north. On the night of December 2, 1943, Bari harbor was crowded with shipping. A German air raid was sudden, swift, and savage. Among the 17 vessels sunk, one contained a cargo of chemical warfare agents, including mustard gas. As reported by Wiltse:

> Undetermined amounts of the gas were held in solution in oil that was floating on water. Of the more than 800 casualties hospitalized after the raid, 628 suffered from mustard gas exposure; 69 deaths were attributed in whole or in part to this cause. Medical officers and aidmen treating the casualties were unaware of the presence of the gas, which diluted sufficiently to be undetected by odor. In the belief that the casualties covered with oil were suffering from exposure and immersion, they were wrapped in blankets, still in their oil-soaked clothing, given hot tea, and left as they were for 12 to 24 hours while the more urgent blast injuries and surgical cases were treated.
>
> Those with the energy and will to clean the oil from their own bodies suffered no serious damage, but the remainder suffered varying degrees of mustard burns. Eyes began to burn about 6 hours after exposure, and were so badly swollen in 24 hours that many of the patients thought themselves blind. The first death occurred without warning 18 hours after exposure.
>
> About 90% of the gas casualties were American, the bulk of them merchant seamen.[11]

This catastrophe is confirmed in the medical history of the 26th General Hospital. This United States Army Air Force installation was in transshipment from Tunisia to Italy, and was to go into operation in Bari in an old, suitably refurbished "ospedale." However, all of the 26th General's equipment was aboard another Liberty ship, the *Samuel S. Tilden*, sunk in the same raid. According to this account:

> During the evening of 2 December 1943, a number of enemy aircraft estimated at approximately 30 planes carried out a

> bombing attack at Bari . . . 17 ships were sunk and there were 1644 casualties, including 442 deaths. One of the ships carried chemical warfare agents, and as a result of the damage to it, mustard gas escaped and produced casualties which accounted for 10% of the deaths.[12]

These casualties were treated at British installations and by American physicians with borrowed beds. All other documents pertaining to this incident remain classified.

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FOR REBUILDING AMERICA'S CHEMICAL DETERRENT

(*The following letter arrived too late for inclusion in the Letters section. It was sent in reply to a letter from the Editor to Senator D'Amato.*)

TO THE EDITOR: I share your horror and revulsion at the thought of chemical warfare. I strongly support our efforts, therefore, to achieve Soviet compliance with the 1925 Geneva Protocol banning the use of chemical and biological weapons and the 1972 Biological and Toxin Weapons Convention which prohibits the mere possession of biological and toxin weapons.

Indeed, I am a cosponsor, along with 35 of my colleagues, of Senate Resolution 201, a resolution expressing the sense of the Senate that the United States should urge other governments to conduct their own investigations of suspected chemical warfare, should assist the United Nations in gaining access to areas where chemical and toxin weapons use is suspected, and should negotiate with the Soviet Union to strengthen existing agreements on chemical, biological, and toxin weapons. I believe this effort is critical to our arms control efforts because it involves the oldest arms control treaty to which both the United States and the Soviet Union are parties.

I was torn, therefore, by the proposed resumption of U.S. chemical weapons manufacture. I voted to fund new production only after long study of the issue. In the final analysis, I was convinced that we need a modern, safe chemical deterrent capability. Passive defensive measures are simply not enough.

The key factor is the presence of millions of civilians in the immediate vicinity of any battle between NATO and Warsaw Pact forces in Europe. More than 30% of the 62 million citizens of West Germany live within 100 kilometers of the inter-German border, the area in which combat will be immediate, high intensity, and devastating. These nearly 20 million German citizens are not protected by any passive defensive gear we may provide our troops. They will not be evacuated because there won't be time and because the roads will be filled with NATO troops advancing to their battle positions. These civilians will be totally exposed to lethal nerve gas blown by the wind from the areas Soviet forces have targeted for chemical strikes. Their only safety lies in our ability to deter chemical attack. If our deterrent fails, hundreds of thousands will certainly die horrible deaths.

The other major factor involved is that, without a credible chemical deterrent, our only recourse if chemical weapons are used against us in massive amounts in the opening stages of a war is to resort to the use of nuclear weapons. Otherwise, we will certainly be defeated. This is a choice we must never allow ourselves to be forced to make. There is, of course, a third option: to rebuild America's chemical deterrent. I endorsed that choice and I am confident that history will prove it to be the right choice.

ALFONSE D'AMATO
United States Senator

Diffuse malignant peritoneal mesothelioma presenting as acute appendicitis

GITA RAMASWAMY, MD, UDAYAN B. SHAH, MD, VICTOR TCHERTKOFF, MD

Malignant mesothelioma, an uncommon occupational disease associated especially with exposure to asbestos, is being more frequently diagnosed due to increased awareness. Malignant peritoneal mesotheliomas are rarer than pleural mesotheliomas. We report a case of diffuse peritoneal mesothelioma whose clinical presentation mimics acute appendicitis.

CASE REPORT

A 72-year-old man was admitted to Metropolitan Hospital Center complaining of abdominal distension, severe right lower quadrant abdominal pain and tenderness. The patient was referred from a psychiatric institution, and an adequate past history could not be obtained.

X-ray film of the abdomen revealed dilated loops of bowel with numerous air fluid levels. Chemistry profiles were normal, except for a moderately elevated lactic dehydrogenase of 860 mg/dL. The hemogram revealed a hematocrit of 45.8% and a WBC count of 20,000/mm^3 with a slight shift to the left. A preoperative diagnosis of acute appendicitis with possible perforation and paralytic ileus was made. At laparotomy, 7 liters of serosanguinous ascitic fluid was evacuated. The entire peritoneal cavity was studded with numerous plaque-like and nodular tumor masses. The omentum was markedly thickened and matted. The appendix appeared swollen and congested. An appendectomy was performed.

After surgery the patient developed spiking fever due to a right lower lobe pneumonia. Despite appropriate antibiotic and supportive therapy, he died on the 12th hospital day.

Pathologic findings. The surgically removed appendix measured 7 cm in length with attached mesenteric fat which appeared thickened and firm. On sectioning, the distal half of the appendiceal lumen appeared dilated and filled with translucent mucoid material. There was marked narrowing of a 0.8-cm segment of the appendix proximal to the dilated distal segment.

Microscopic examination showed infiltration of the periappendiceal adipose tissue, serosa and muscularis of the appendix by pleomorphic neoplastic cells. The cells were polyhedral to round with opaque eosinophilic cytoplasm, round to oval nuclei and prominent nucleoli. Bizarre mitosis and tumor giant cells were frequent (Fig 1). The predominant arrangement consisted of solid sheets of cells. In other areas, the cells appeared noncohesive, with distinct cytoplasmic margins, surrounded by a delicate fibrous connective tissue stroma. Peripherally situated indented nuclei were observed in a few cells, superficially resembling signet ring cells of an adenocarcinoma (Fig 2). There was no evidence of acinar or glandular arrangement, papillary formations or large areas of tumor necrosis. Mucicarmine and PAS stains were negative in the tumor cells, however, alcian blue demonstrated the presence of intracytoplasmic and extracellular acidic mucopolysaccharides. Tumor giant cells resembling rhabdomyoblasts were seen but cross striations were absent on PTAH stain. The mucosa of the appendix distal to the narrowing revealed flattening of the epithelium secondary to intraluminal accumulation of thick gliary mucus.

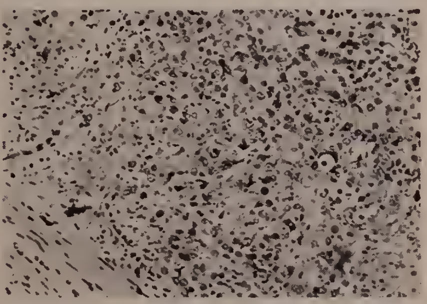

FIGURE 1. Anaplastic tumor cells infiltrating wall of appendix (hematoxylin and eosin stain, original magnification X350).

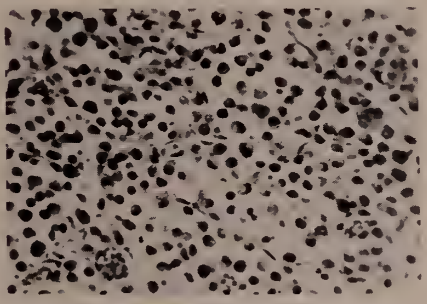

FIGURE 2. Tumor cells with eccentrically placed nuclei and abundant cytoplasm (hematoxylin and eosin stain, original magnification X350).

At autopsy, the peritoneal cavity contained 9 liters of serosanguinous fluid. There was extensive involvement of the omentum, mesentry, peritoneal surfaces of the abdominal viscera and both domes of the diaphragm by gray white tumor. Both visceral and parietal pleurae were focally involved with extension into the interlobar fissures; however, there was no severe encasement of the lungs by tumor. The hilar paratracheal, para-aortic retroperitoneal lymph nodes, and vertebral bone marrow showed nodular gray-white metastatic tumor masses. A thorough search of all viscera excluded any other primary neoplasm.

Microscopic sections of the tumor at autopsy showed identical features to those seen in the surgical specimen of the appendix. Multiple sections from the lungs, prostate, thyroid, and kidneys ruled out any occult primary in these organs. Sections from the interlobar fissures of the lungs showed extension of tumor along subpleural and perivascular lymphatics. There was focal infiltration of the superficial myocardium at the site of visceral pericardial involvement. The serosal surfaces of all the abdominal viscera contained tumor with focal infiltration into the subjacent parenchyma. Segments of intestine that were grossly normal had microscopic evidence of tumor in their serosa.

Electronmicroscopy. The tumor cells had abundant cell surface microvilli, interdigi-

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From the Department of Pathology, Metropolitan Hospital Center, New York, New York.

Address correspondence to Dr Tchertkoff, Professor of Pathology and Director of Laboratories, Metropolitan Hospital Center, 1901 First Ave, New York, NY 10029.

tating in some areas with those of adjoining cells, numerous intercellular tight junctions, intracytoplasmic vacuoles, many with microvilli and occasional tonofilaments (Fig 3). Intracellular glycogen and mitochondria were abundant. A variable amount of collagen was present in the intercellular spaces.

DISCUSSION

Diffuse peritoneal mesotheliomas are rare primary neoplasms of the peritoneum. Largely due to the tissue culture studies carried out by Maximow,[1,2] Sano et al,[1] Stout and Murray,[3] the mesothelial cell origin of mesotheliomas has been confirmed.

There is significant epidemiological evidence that exposure to asbestos may be associated with subsequent development of malignant mesotheliomas. In an occupationally exposed population studied by Selikoff et al,[4] 7% of all deaths were due to mesotheliomas. McDonald and McDonald[5] in their exhaustive study on this subject concluded that two thirds of patients with mesotheliomas had a history of exposure to asbestos.

As with pleural mesotheliomas, there is a distinct male predominance of peritoneal mesotheliomas, occurring chiefly in the fourth to the eighth decade of life. Seventy-five percent of patients in some series were above the age of fifty. The patients generally have abdominal discomfort, pain, distension or recent weight loss. Some patients have partial intestinal obstruction or massive ascites.

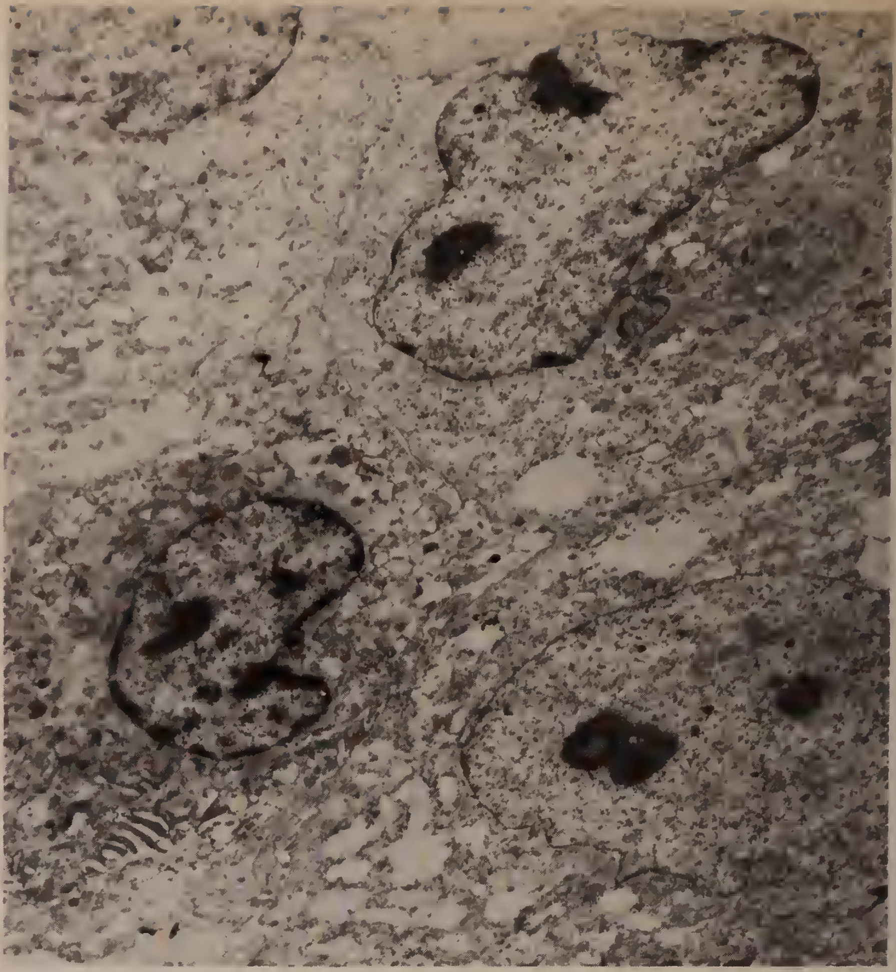

FIGURE 3. Low-power electron photomicrograph of tumor cells. Note cell surface microvilli and light intercellular junctions.

The microscopic findings of diverse histologic patterns of this tumor presents a diagnostic problem to the surgical pathologist. Diffuse peritoneal mesothelioma may easily be mistaken for metastatic adenocarcinoma, when it has an epithelial or glandular pattern; or for soft tissue tumor when it is in a sarcomatous form. It may be erroneously diagnosed as benign when collagenous tissue is the sole component in a biopsy. The differentiation between diffuse malignant mesothelioma and mesothelial hyperplasia is difficult to impossible in a small biopsy. Widely disseminated mesotheliomas are often indistinguishable from diffuse carcinomatosis and had led some to believe that the diagnosis of malignant mesothelioma can be made with certainty only if autopsy reveals no other primary malignancy.

Nevertheless there are some characteristic microscopic features that establish the diagnosis of mesotheliomas. These are the biphasic (epithelial and sarcomatous) pattern in the same tumor; presence of intracellular and extracellular acidic mucopolysaccharides (detected by the Alcian blue stain)[7,8] and characteristic epithelial ultrastructural features.[8]

Malignant peritoneal mesothelioma tends to spread diffusely in the abdomen with generally massive involvement of the omentum. The wall of the gastrointestinal tract may be penetrated to varying depths with envelopment of the liver, spleen and focal subcapsular invasion. There is usually extension to the undersurface of the diaphragm with occasional through and through penetration and pleural involvement. There may be massive retroperitoneal spread surrounding the pancreas and renal capsule. Extension into the anterior abdominal wall is generally limited into scars of previous laparotomies.

Metastases via the lymphatics have been reported in approximately 50% of the cases of peritoneal mesotheliomas with spread to the mesentric, peripancreatic and para-aortic nodes. The inguinal and thoracic nodes may on occasion also be involved.

The route of pleural and pericardial involvement is generally attributed to direct extension through the diaphragm as was present in this case. However, pleural and pericardial metastasis may be present without diaphragmatic involvement.

Since mesotheliomas are associated with effusions, cytologic and chemical studies for hyaluronidase may be undertaken to enhance diagnostic accuracy.[9-11]

Malignant peritoneal mesotheliomas are generally rapidly fatal within a year; however, occasional survivals up to six years after diagnosis have been reported. Review of the literature has not shown any consistent correlation between cell type, histologic pattern, or degree of differentiation and length of survival. The poor prognosis of mesotheliomas may be partly attributed to the fact that many patients seek medical attention when the disease is far advanced, rendering the lesion unresectable. Intracavitary installation of radioactive gold and ^{32}P have been noted to produce remissions in some patients. Chemotherapeutic agents have been used with encouraging results in some advanced cases.[12]

In conclusion, the finding of diffuse peritoneal mesothelioma, a rare tumor, resulting in narrowing of the appendix and presenting clinically as acute appendicitis are unusual features in this case.

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Malignant epithelial mesothelioma of the anterior mediastinum

JOSEPH A. TAGLIAMONTI, MD, KAITY YANNOPOULOS, MD, LAWRENCE S. KRYLE, MD

A patient with malignant epithelial mesothelioma of the anterior mediastinum had an unusual presentation consisting of congestive heart failure, pulmonary hypertension, and acute myocardial ischemia. The patient developed coronary artery occlusion caused by extrinsic tumor compression resulting in diminished coronary artery flow, acute myocardial ischemia, and sudden death. In addition, the tumor had encircled the aorta and pulmonary arteries resulting in symptoms of right ventricular failure that did not respond to the usual therapy. Conventional x-ray studies and echocardiogram only disclosed pericardial effusion with no irregularity of the pericardial outline. The diagnosis was established by postmortem examination.

CASE REPORT

A 44-year-old woman was admitted to St. Francis Hospital because of shortness of breath. Her past history was significant in that she claimed to have had rheumatic fever at age 10 followed by a heart murmur.

Eight months prior to this admission, the patient went to her physician complaining of neck pain and shortness of breath when leaning forward. She was treated unsuccessfully with intermittent neck traction and salicylates. She also sought chiropractic treatment.

The shortness of breath that precipitated the hospitalization became more intense three weeks prior to admission and was accompanied by swelling of the ankles and extreme fatique. There was a 7.2-kg (14-lb) weight loss over a six-month period as well as menstrual irregularities. During this time, both the patient and her family realized that she became very nervous and high-strung.

Physical examination at the time of admission revealed a middle-aged woman in moderate respiratory distress. The neck veins were distended and filled from below. The thyroid was slightly enlarged but soft. A hepatojugular reflux was identified. There was dullness on percussion of the right lower chest with diminished breath sounds. Bilateral basilar rales were heard over both lung fields posteriorly. The heart tones were of good quality. The rhythm was regular. Heart rate was 100 beats per minute. A grade 2/6 systolic murmur was heard along the left sternal border together with a third heart sound gallop. The liver was palpable 2 cm below the right costal margin. A palpable fluid wave was elicited. There was 2+ pretibial pitting edema. All arterial pulses were readily palpable. Neurologic examination disclosed no abnormalities. There was marked clubbing and cyanosis of the fingers and toes. Pelvic examination revealed enlargement of the uterus.

Laboratory data were as follows: normal CBC; sedimentation rate 9; C-reactive protein was 3+; antistreptolysin titer was negative; urinalysis showed a few red blood cells but the patient was menstruating; electrolytes, BUN, and serum glucose values were normal; mild elevations in alkaline phosphatase and LDH were noted; thyroid studies were normal and serum digoxin level was 0.9 ng/mL.

Chest x-ray showed generalized cardiac enlargement with relatively clear lung fields (Fig 1).

Electrocardiogram revealed complete right bundle branch block and left anterior hemi-

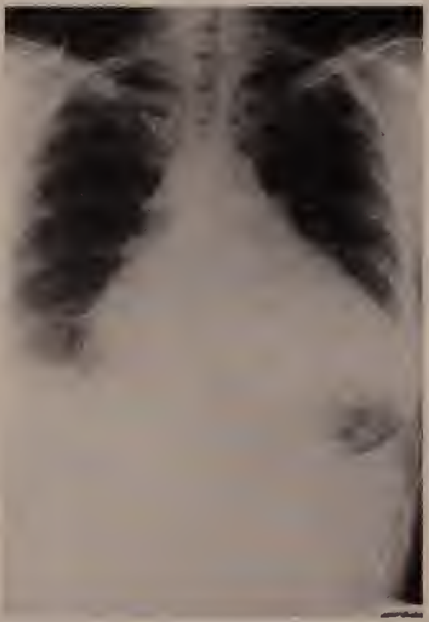

FIGURE 1. Chest x-ray shows generalized cardiac enlargement with relatively clear lung fields. Cardiac shadow is compatible with pericardial effusion. No definite masses are noted.

From the Departments of Pathology (Drs Tagliamonti and Yannopoulos) and Medicine (Dr Kryle), St. Francis Hospital, Roslyn, New York.

Address correspondence to Dr Tagliamonti, Associate Pathologist, St. Francis Hospital, Roslyn, NY 11576.

block. Echocardiogram showed no cardiac chamber enlargement, 300 mL of pericardial effusion, and mild mitral valve prolapse.

The patient was treated with digoxin and diuretics. She improved substantially and lost about 4 kg of body weight. Ambulation was well tolerated and the patient was discharged in seven days for outpatient care.

Several weeks after discharge, she experienced dyspnea, weakness, and syncope. She failed to respond to large doses of oral and parenteral diuretics together with manipulation of the dose of digoxin.

The patient was readmitted one month after the first admission because of increasing dyspnea and orthopnea. Physical findings were essentially the same as the earlier admission. Again, a prominent third heart sound was heard in early diastole. A faint systolic murmur was present along the lower left sternal border. The neck veins were moderately enlarged. A palpable liver was present. The lungs were clear to percussion and auscultation. There was 2+ pitting presacral edema. Fingernails and toenails were cyanotic and clubbed.

Laboratory data revealed a creatinine phosphokinase (CPK) level of 319 that rose to 1,170 the following day; CPK-MB was positive; lactic dehydrogenase (LDH) was markedly elevated but the flip was negative; BUN was normal; digoxin was 1.6 ng/mL; arterial blood gases were: pO_2, 81; pCO_2, 23; and arterial oxygen saturation, 93.8%.

The day after admission, the patient became lethargic and a few minutes later experienced a grand mal seizure. She then became unresponsive and deeply cyanotic with no pulse detected. Cardiac resuscitation restored blood pressure and pulse but the patient remained cyanotic and incoherent. EKG tracings showed varying degrees of AV block, marked elevation of the ST segments over the anterior and septal leads with a QS pattern in the inferior leads. A diagnosis of anterior wall myocardial infarction was made and substantiated by marked elevation of the CPK, SGOT, and LDH. On the following day, she experienced multiple cardiorespiratory arrests and expired, despite resuscitative efforts.

Pathologic findings. The pleural cavity had a smooth lining. Each hemithorax contained 800 mL of clear fluid. The pericardial sac contained 300 mL of clear fluid. The peritoneal surfaces were smooth with 4,000 mL of clear fluid within the pleural cavity. In addition, the head, neck, and upper trunk exhibited marked subcutaneous edema as did the conjunctivae. The heart weighed 470 g. Arising above the right atrium there was a firm, pinkish-white, irregular-surfaced neoplasm surrounding and compressing the superior vena cava, the pulmonary arteries, the aorta and great vessels. (Figs 2, 3). The right and left coronary arteries were compressed proximally at the ostia by the neoplastic process. The tumor mass extended laterally to the hilar regions bilaterally, but did not invade the lung parenchyma. It measured 12 cm in its greatest dimension. The myocardium exhibited an extensive area of fibrosis and paleness over the septum and anterior wall of the left ventricle. Both the right and left ventricular walls of the heart were hypertrophied.

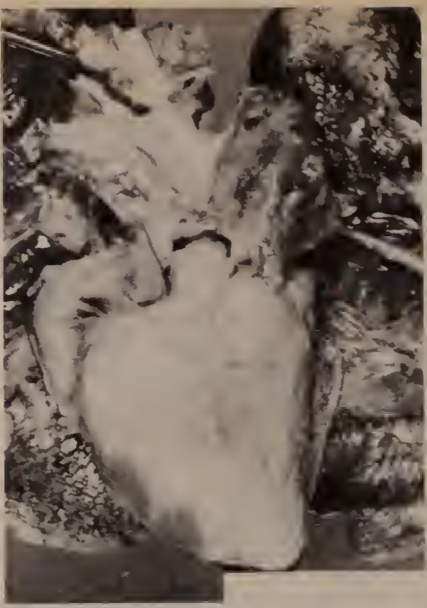

FIGURE 2. At autopsy, a diffusely infiltrating lesion is noted involving the main vessels and bifurcation.

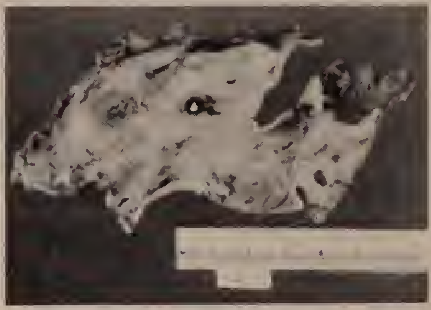

FIGURE 3. On cross sections, the diffuse infiltration of tissue around pulmonary artery, aorta, and aortic arch extending to proximal segments of the coronary arteries is noted with compression, especially of pulmonary artery.

Microscopic sections revealed an infiltrating neoplastic process with extensive areas of necrosis, hemorrhage, and degeneration. The neoplastic cells were cuboidal, cylindrical, or polyhedral in shape. They exhibited an increased nuclear cytoplasmic ratio, vesicular nuclei, prominent chromatin pattern and mitotic activity. The neoplastic cells formed tubular structures, strands, or groups separated by a fibrous stroma (Fig 4). Lymphatic vessel and perineural lymphatic involvement were focally encountered. Sections of the coronary arteries, aorta, pulmonary artery, and the main bifurcation showed neoplastic cells involving the adventitia with an intact media and intima. The lumina of the coronary arteries were compressed; however, there was no evidence of thrombosis or occlusion.

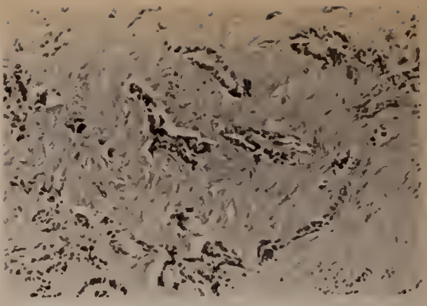

FIGURE 4. Microscopic sections exhibit tubular structures lined by cuboidal or cylindrical malignant neoplastic cells.

Sections of the right and left ventricles showed areas of fibrosis replacing normal myocardial fibers. Extensive areas of early ischemic change were present throughout the myocardium and were demonstrated by special stains.

Sections of the lung parenchyma adjacent to the tumor showed focal involvement of the pleura by neoplastic cells but there was no involvement of lung parenchyma. No evidence of metastasis was seen in the other organs examined.

Additional findings included acute passive congestion of the viscera and a submucous uterine leiomyoma.

Discussion

The case demonstrates the difficulty in the antemortem diagnosis of a mesothelioma located in the anterior mediastinum. Chun et al[1] reported a case of primary pericardial malignant epithelial mesothelioma; however, a prominent anterior mediastinal mass was seen on chest x-ray film. The patient presented with pericardial effusion. X-ray films showed a large cardiac silhouette with regular contours and heart failure without obvious etiology associated with pulmonary hypertension, hepatomegaly, anasarca, chest pain, and superior vena cava syndrome. The tumor was not seen on chest x-ray film or sonogram. There was no bizarre cardiomegaly as described in the case of Forrest and Kozonis.[2] A pericardial tap was not performed, however, the neoplasm was confined to the external surface of the pericardium. When pericardial fluid has been studied for malignant cells the yield of diagnostic material has been poor.[3]

The patient had no exposure to asbestos.[4,5] However, her husband was intermittently associated with asbestos, working as an oil-burner repairman. He worked in areas that were heavily insulated with asbestos, but he did remove all his clothing before returning home and changed from his work clothes into street clothes. The patient did not wash her husband's work clothes. It is not known whether or not there was any asbestos exposure at the school where the patient was employed. After inspection of the school, there were no loose ceilings or asbestos deposits.

The outstanding feature of this case was that there was evidence of severe dyspnea, orthopnea, weakness, and weight loss. Chest x-ray failed to reveal evidence of increased left ventricular failure as shown by the absence of Kerley B-lines and evidence of increased pulmonary artery or veins on x-ray. This certainly should have aroused the suspicion that more was occurring than was thought of originally. No evidence of rheumatic heart disease was found at autopsy. The clubbing and cyanosis of the finger nails undoubtedly were caused by obstruction of the pulmonary artery by the tumor and as a result the oxygen saturation to the tissue was low. A computed tomography scan, which would have been diagnostic,[6] was not performed because of the patient's weakened condition.

Acknowledgments. The authors thank Frances Koltusz-Plompen for secretarial assistance, and Ernest Bartell for the photographic illustrations.

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Myocardial rupture following intracoronary thrombolysis

GERALD HOLLANDER, MD, HERSHEL OZICK, MD, MARIO ANSELMO, MD, MICHAEL SANDERS, MD,
EDGAR LICHSTEIN, MD, ALVIN GREENGART, MD

Intracoronary thrombolytic therapy during the early stage of acute myocardial infarction has recently been reported.[1,2] The full benefit and complications of this procedure are still not well defined. We describe a patient who experienced myocardial rupture soon after such therapy.

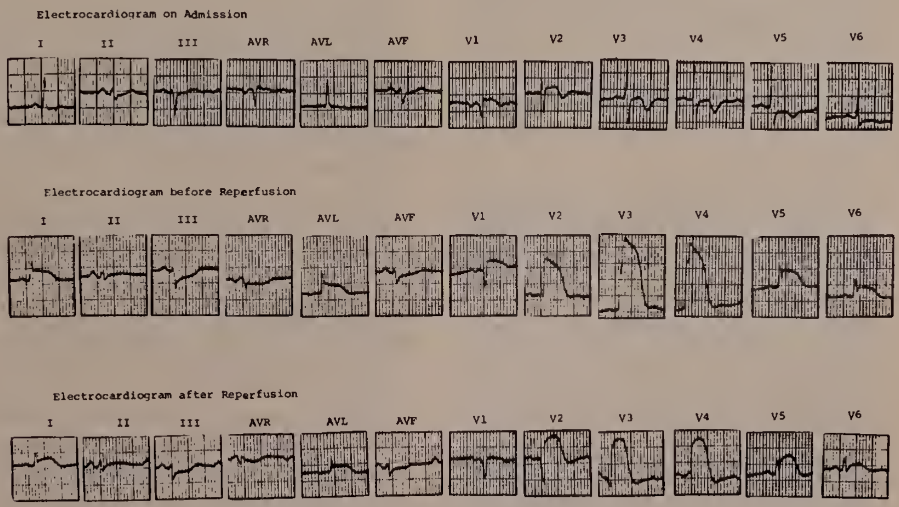
CASE REPORT

A 61-year-old man was admitted to the coronary care unit because of an episode of substernal pressure radiating down his left arm that occurred 12 hours before admission. Five days before admission, the patient experienced episodes of chest pressure while performing household chores. These episodes lasted several minutes and were relieved by rest. The episode of pain that prompted admission occurred at rest and lasted one hour. The patient had smoked two packs of cigarettes per day for 40 years. There was no history of hypertension, diabetes, hyperlipidemia, or previous heart disease. There was a strong family history of premature coronary artery disease.

On admission to the coronary care unit, the heart rate was 88 per minute and regular, blood pressure 140/90 mm Hg, and respirations 18 per minute. An S4 gallop was heard. The chest roentgenogram was within normal limits. The initial electrocardiogram (Fig 1) showed normal sinus rhythm with ST-T wave changes consistent with anterior wall ischemia or infarction. Small initial q waves were seen in lead V_2. Pertinent laboratory data included hematocrit 45%, WBC count 15,000/mm^3 without a shift to the left, hemoglobin 15.5 g/dL, BUN 12 mg/dL, and glucose 110 mg/dL. Electrolyte values were within normal limits and the creatinine phosphokinase (CPK) was 35 (normal, 35 to 239).

Twelve hours after admission, the patient complained of severe chest pain. The electrocardiogram at this time showed massive ST elevations in the precordial leads (Fig 1).

Within an hour after the onset of ST elevation, the patient was taken to the catheterization laboratory. Coronary arteriography revealed complete occlusion of the left anterior descending artery proximal to the first septal perforator (Fig 2). Left ventriculography, performed with a pigtail catheter, showed a large area of apical dyskinesia. There was no change in the degree of occlusion after the infusion of intracoronary ni-


Electrocardiogram on Admission
I
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Electrocardiogram before Reperfusion
I
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III
AVR
AVL
AVF
V1
V2
V3
V4
V5
V6
Electrocardiogram after Reperfusion
I
II
III
AVR
AVL
AVF
V1
V2
V3
V4
V5
V6

FIGURE 1. Patient's electrocardiograms at the time of admission, when acute chest pain and ST segment elevation developed and after reperfusion.

From the Divisions of Cardiology (Drs Hollander, Ozick, Sanders, Lichstein, Greengart) and Pathology (Dr Anselmo), Maimonides Medical Center, Downstate Medical Center, SUNY, Brooklyn, New York

Address correspondence: to Dr Hollander, Director, Coronary Intensive Care Unit, Maimonides Medical Center, 4802 10th Avenue, Brooklyn, New York 11219

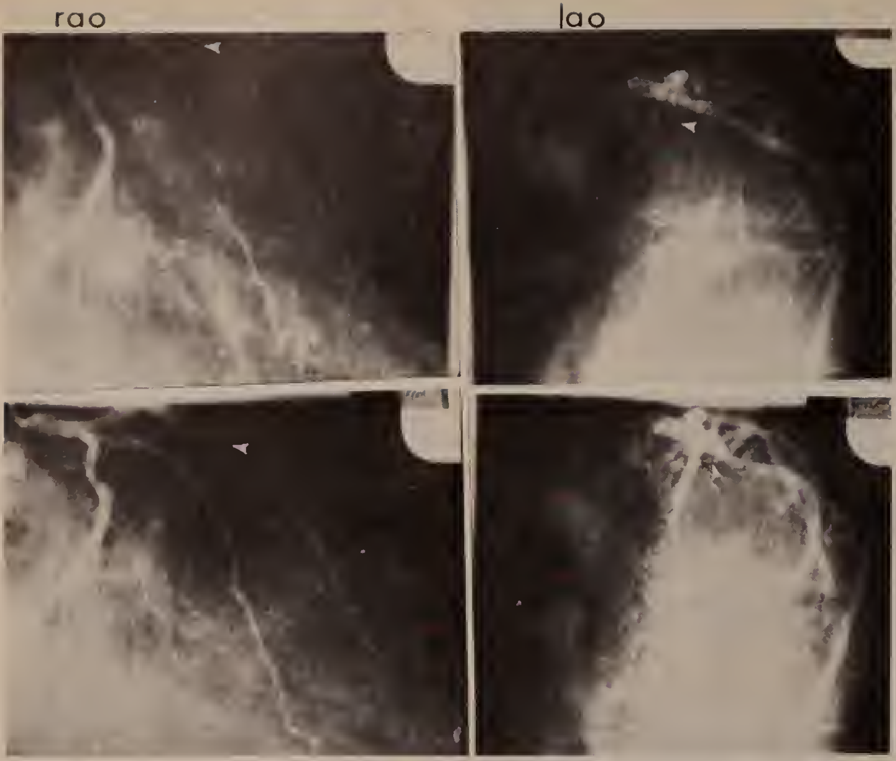

FIGURE 2. Left coronary angiogram before (upper panel) and after (lower panel) reperfusion. rao = right anterior oblique, lao = left anterior oblique. Arrow indicates site of proximal left anterior descending occlusion.

troglycerin. A 10,000-unit bolus of streptokinase was then infused in the left coronary artery, followed by a continuous infusion of 2,000 units per minute. After 30 minutes, the left anterior descending artery was patent with residual critical stenosis (Fig 2). Streptokinase infusion was continued for a total of 60 minutes.

After the completion of the procedure, the patient no longer complained of chest pain. His blood pressure was 120/80 mm Hg. His pulse was 80 per minute and regular. There was no significant change in the ST segments, and the QS pattern was present in leads V_1-V_3 (Fig 1). The administration of heparin, 1,000 units/hour, was started, and the patient was returned to the coronary care unit in good condition.

Twelve hours after streptokinase therapy, the patient suddenly became hypotensive and died in electromechanical dissociation despite resuscitative efforts.

Postmortem examination revealed a fresh hemorrhagic transmural infarct involving the interventricular septum and anterior wall and two areas of perforation through the anterior wall (Fig 3).

Microscopic examination of the infarcted area showed hyalinization and loss of striation of the myocardial fibers, karyolysis of muscle nuclei, and neutrophilic infiltration, suggesting that the infarct was at least 24 hours old. Also noted was extensive hemorrhage within the area of infarction (Fig 4). The coronary arteries showed a moderate degree of atherosclerosis. No thrombus was seen within the left anterior descending artery.

DISCUSSION

The pathophysiologic factors involved in myocardial infarction remain unclear. Approximately 80% of acute myocardial infarctions are associated with total coronary occlusion.[3] A contributory role of coronary artery spasm was suggested by Oliva and Breckenridge.[4] Thrombosis at the site of coronary artery obstruction has recently been emphasized, and nonsurgical reperfusion of the acutely occluded infarct-related coronary artery has been demonstrated by several observers.[1,2]

Clear-cut benefit of coronary artery reperfusion has not been proved. Generally, with early reperfusion, there is rapid evolution of the electrocardiographic Q wave and rapid release of creatinine phosphokinase from the myocardium. These sequelae make it difficult to demonstrate myocardial salvage. Despite this difficulty, effective myocardial salvage has been suggested by improved myocardial uptake of thallium 201 and by improved global and regional left ventricular function.[2,5-7] This improvement in function appears to be related to the timing of reperfusion and, for this reason, most studies limit reperfusion to patients seen within three to six hours after the onset of myocardial infarction.[1,2]

The complications reported with thrombolytic therapy in acute myocardial infarction have been those related to cardiac catheterization, coronary angiography, and systemic bleeding related to anticoagulation. An additional potential complication involves reperfusion injury to the infarcted tissue with conversion of a bland infarct to a hemorrhagic infarct. This may cause extension of the area of infarction beyond the borders of the initial necrosis and possibly even cardiac rupture. Investigations by Fishbein et al[8] suggest that reperfusion-induced hemorrhage is localized to the area of initial necrosis, and, therefore does not produce a larger infarct size. Mathey et al[9] reported hemorrhagic infarction in three patients treated with early reperfusion after infarction. However, the hemorrhagic area did not extend beyond the borders of initial infarction. To the best of our knowledge, myocardial rupture following acute reperfusion with streptokinase has not been previously reported.

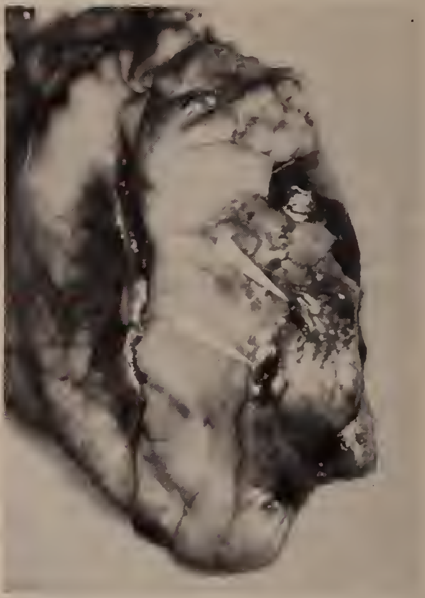

FIGURE 3. Photograph of the left ventricle showing areas of myocardial rupture (arrows).

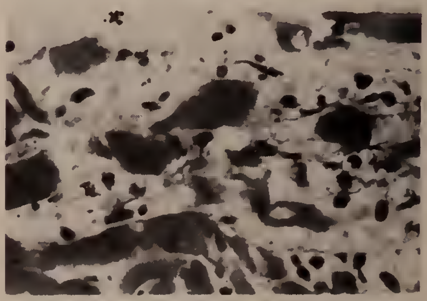

FIGURE 4. The interstitium shows ghostly outline of RBCs, which were diffusely present in the infarcted area.

Acknowledgments. We wish to thank Amy Harrison and Shaye Komitau for their assistance in preparing this manuscript.

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Acute appendicitis presenting as cholestatic jaundice

GREGORY MEYER, MD, JOHN PAUL LANDI, MD, CAPECOMORIN S. PITCHUMONI, MD

Cholestatic jaundice of sepsis is a well-recognized entity that has been ascribed to numerous organisms which originate from virtually any septic focus.[1-3] We describe a patient with cholestatic jaundice resulting from asymptomatic acute appendicitis.

CASE REPORT

A 40-year-old motel manager with no previous medical problems was admitted with a four-day history of weakness, fever, and intermittent shaking chills. He was severely anorectic and had lost his appetite for cigarettes. He denied nausea, pruritis, and changes in bowel habit but had noted darkening of his urine. He had been taking no medications prior to the onset of these symptoms.

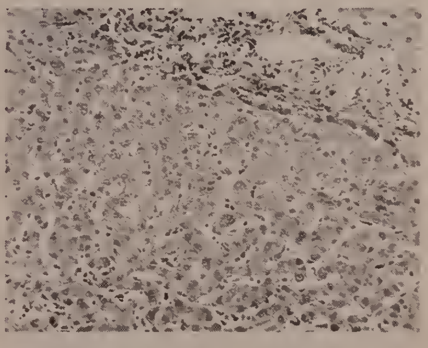
He appeared comfortable except for intermittent bouts of shaking chills. During one of these episodes, oral temperature was recorded to be 39°C with pulse 112 per minute and blood pressure 106/60 mm Hg. Sclerae were deeply jaundiced. The lungs were clear. Tachycardia was noted. The abdomen was soft. Rectal examination revealed no tenderness, and stool was negative for occult blood. Pertinent laboratory results included WBC count of 6,600 with left shift (28 band forms, 60 segmented forms, and 2+ toxic granulations), hemoglobin 15 g/dL, alkaline phosphatase 157 IU/L (normal 30-115), and total bilirubin 5.9 mg/dL with 5.4 mg/dL direct acting. Serum amylase and SGOT levels were normal. Supine and upright films of the abdomen were normal, and abdominal ultrasound showed a normal gallbladder without evidence of stone or dilatation of the extrahepatic bile ducts. A diagnosis of acute cholecystitis was considered despite the negative results. Percutaneous transhepatic cholangiography was attempted but cannulation of the bile ducts was unsuccessful on three attempts.

By the second hospital day the total bilirubin had increased to 7.8 mg/dL with minimal change in alkaline phosphatase (131 IU/L). Intravenous ampicillin therapy was initiated, but the patient continued to have severe shaking chills. On the third hospital day, laparotomy revealed an acute gangrenous appendix with incipient perforation. The gallbladder appeared normal and intraoperative liver biopsy showed no diagnostic abnormalities. Cultures of the appendix produced a heavy growth of *Klebsiella pneumoniae* and a light growth of *Bacteroides fragilis.* Blood cultures drawn on admission were negative. The patient had an unremarkable recovery with prompt and complete resolution of the jaundice. Liver function tests performed a week after surgery indicated persistence of cholestasis, but a month later test results were completely normal.

DISCUSSION

Although jaundice as a postoperative complication of appendectomy has frequently been reported,[3] acute appendicitis presenting as cholestatic jaundice in an adult is unusual. The diagnosis of acute appendicitis was unexpected on the basis of clinical features and results of investigations, but the diagnosis of cholestatic jaundice secondary to sepsis, probably from a focus in the abdomen, was considered. The appendix was shown to be the focus at laparotomy.

Jaundice results from cholestasis induced by sepsis. Direct bacterial action has been largely discounted, and cholestasis cannot be ascribed solely to circulating endotoxins because jaundice has been seen in association with septicemia from non-endotoxin-producing gram-positive organisms.[3] It has been suggested that other unidentified bacterial products may be responsible. Consistent with this is the fact that in many cases, as with ours, bacteremia is not demonstrated. Liver histology is frequently normal but may show mild cholestasis or a host of other changes such as mononuclear cell portal infiltrates and focal hepatitis. Peak bilirubin is usually 5 to 10 mg/dL with 75% to 80% direct acting, and alkaline phosphatase is elevated in about 50% of cases but does not exceed



Liver biopsy specimen at surgery shows no diagnostic abnormalities.

From the Division of Gastroenterology, Misericordia Hospital Medical Center, The Bronx, New York.

Address correspondence to Dr Pitchumoni, Chief, Division of Gastroenterology, Misericordia Hospital Medical Center, 600 East 233rd St, Bronx, NY 10466.

three times the normal value. Serum transaminase levels are usually normal or slightly elevated. The clinical picture, treatment, and prognosis are essentially those of the underlying sepsis.

This case emphasized that jaundice is not always indicative of a primary hepatic or biliary tract disease. An extrahepatic source of sepsis should be rigorously sought in any febrile jaundiced patient with normal or near normal serum transaminase levels and negative ultrasound examination of the gall bladder.

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Perforative appendicitis in the third trimester of pregnancy

MARK SPITZER, MD, IRWIN H. KAISER, MD

Acute appendicitis is the most common extragenital surgical complication of pregnancy. The maternal mortality rate for all cases of appendicitis in pregnancy is 0.01% to 0.4%, and overall fetal mortality is 8.5% to 8.7%.[1,2]

McComb and Laimon[3] in 1980 collected 171 cases of appendicitis from the literature. Fetal mortality was 10/145 (7%) in pregnancies with unperforated appendicitis and 8/27 in cases where the appendix was perforated, more than a fourfold increase. Despite the equal distribution of appendicitis in the three trimesters, their review of 36 cases of appendiceal perforation disclosed that 25 occurred in the third trimester.

It is our intention to report a case and review the literature since 1951 to see if any conclusions can be drawn to improve the management of this entity.

CASE REPORT

A 33-year-old woman, para 2-0-1-2, had an uneventful pregnancy until two weeks prior to admission when she experienced left lower quadrant pain and constipation, without nausea or vomiting. Four days prior to admission the pain became worse. Ampicillin was started for a presumed urinary tract infection. On the day of admission, the patient suddenly felt severe generalized abdominal pain, referred to the left side, which "doubled her over." There was no nausea or vomiting.

On physical examination the patient was diaphoretic and in acute distress. Vital signs were: BP 180/80, pulse 140, respirations 50. Her abdomen was rigid and tender and the skin cyanotic. Fetal heart sounds could not be easily heard because of the patient's agitation. Pelvic examination disclosed a cervix 1 cm dilated and 0.5 cm long with a vertex at −1 station and intact membranes. Hematocrit was 40%. WBC 11,800. A presumptive diagnosis of abruptio placentae was made. Membranes were ruptured, the amniotic fluid was clear, and an internal electrode was applied. The tracing showed a fetal heart rate of 120 with severe decelerations to 80 and poor recovery.

An emergency cesarean section was performed through a vertical midline incision. Upon entering the peritoneal cavity, frank pus was seen; specimens were obtained for culture. A 2,400-g female infant was delivered through a low transverse uterine incision. Apgar scores were 8 at one minute and 9 at five minutes. Venus cord gases were: pH, 6.92; PCO_2, 85; and PO_2, 20.2.

After closing the uterus, the abdomen was explored. A ruptured abscess was identified in the left paracolic gutter, composed of omentum, cecum, and appendix adherent to the abdominal wall. The cecum was of normal configuration but had a complete mesentery. It fell easily back into the right lower quadrant when adhesions were freed. The abscess and appendix were resected, the abdomen was irrigated with cefazolin solution and a drain was placed at the site of the abscess. During the operation the patient was started on ampicillin and clindamycin and after operation gentamicin was begun. Intraoperative cultures grew *Escherichia coli*, nonhemolytic *Streptococcus* and *Bacteroides fragilis*.

The patient recovered well postoperatively. She was never febrile and was discharged 15 days after the operation. The baby also did well.

DISCUSSION

In both the review of the literature and in the case report here, it is evident that delay in diagnosis can lead to disastrous complications. Clearly, if appendicitis is suspected at any stage of pregnancy, exploratory laparotomy is indicated. Many authors[1,4-6] have pointed out that a laparotomy with negative findings does not cause a significant rate of abortion or premature labor even if an incidental appendectomy is performed.

Many authors have voiced their opinion that cesarean section at the time of appendectomy should be undertaken only on obstetric indications.[4,5,7,8] Leslie[9] found several indications for appendectomy combined with cesarean sections, including (1) when there are other obstetrical indications, (2) near term, when immediate delivery lessens the risk to the fetus caused by septic shock, and (3) when access to the appendix must be gained.

It seems that the fetal mortality rate and the rate at which perforative appendicitis precipitates delivery are the critical data necessary to make a valid decision in such cases. In our review of the literature, 43 cases were found with enough information reported to determine the rate at which perforative appendicitis leads to early delivery (delivery soon after the catastrophic event).[3,5-8,10-13] Thirty-three of these 43 patients delivered within several days. The fetal mortality rate was 16/43; maternal mortality was 2/43. On the other hand, no fetal or maternal deaths were reported in 15 cases where the fetus was delivered immediately, either vaginally or by cesarean section.[8,10,11,14,15]

Two other cases were found in the records of Bronx Municipal Hospital. Both mothers and babies lived although both babies were delivered prematurely and one developed hydrocephalus.

From the Department of Obstetrics and Gynecology, Albert Einstein College of Medicine, The Bronx, New York.

Dr Spitzer is now at Long Island Jewish-Hillside Medical Center, New Hyde Park, NY 11042.

Address correspondence to Dr Kaiser, Professor, Department of Obstetrics and Gynecology, Room 501, Belfer Educational Center, 1300 Morris Park Ave, Bronx, NY 10461.

We have been unable to find a previously published report of fetal distress, despite many fetal deaths. One can only assume that fetal status was not routinely monitored in these cases. In fact, fetal status on admission is seldom mentioned, so it is difficult to determine if some of the fetal deaths were preventable.

Finally, the type of incision most commonly used is the muscle-splitting (McBurney) incision, usually over the point of maximal tenderness. This incision usually suffices in routine nonperforative appendicitis, but it may be very inconvenient at times. A low vertical midline incision offers several advantages. It affords adequate exposure for removal of an inflamed appendix and the treatment of other conditions that simulate appendicitis. This is very important in view of the high incidence of false negative diagnosis. It also allows for evacuation of the uterus where indicated.

We conclude that whenever appendicitis is suspected during pregnancy, laparotomy should be immediately performed. In cases of generalized peritonitis during third trimester we recommend this be done through a low vertical midline incision to allow for adequate exposure and, possibly, emptying the uterus. Constant fetal monitoring is warranted until either delivery or stabilization of the maternal status. Immediate delivery should be considered when adequate neonatal support is available, the fetus is viable, and the degree of fetal distress warrants delivery.

Acknowledgments. Kay Anderson, MD and Rosa Gonzalez, MD who were concerned with the care of the patient in this case were kind enough to give their permission for the use of the clinical report.

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Intravenous nitroglycerin and cardiac failure

LAWRENCE A. GOULD, MD

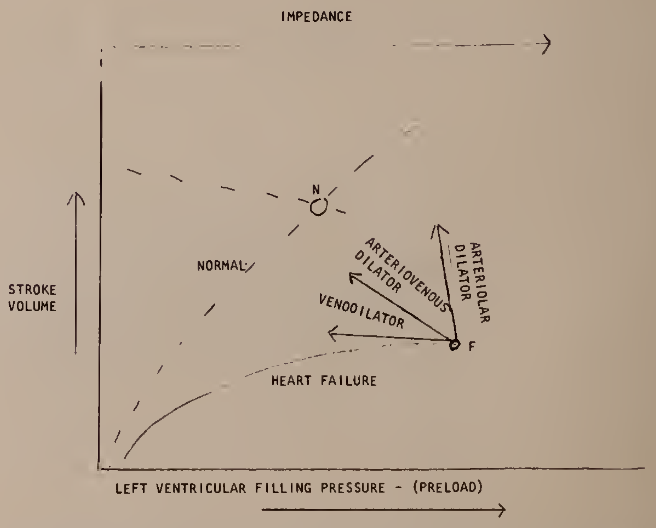
ABSTRACT **Intravenous nitroglycerin is now available for the management of left ventricular failure complicating myocardial function. Other applications include the management of acute left ventricular failure secondary to acute mitral regurgitation or aortic insufficiency as well as acute ventricular septal rupture. The drug can also be used for the treatment of the acute exacerbation of chronic heart failure. Nitroglycerin's dilating actions are maximal on the capacitance vessels and least on the resistance vessels. However the dilating mechanism of nitroglycerin is still unknown. The drug is well tolerated, although headache is a common complication of therapy. A decrease in the arterial oxygen tension, probably due to a ventilation perfusion mismatch, may also be seen.**

(NY State J Med 1984; 84:136–139)

It has now been shown that vasodilator therapy can improve cardiac performance not only in patients in congestive heart failure, but also in patients with valvular regurgitation and acute myocardial infarction. The rationale behind the use of the various vasodilator drugs has evolved from an understanding of the factors that modify the function of the left ventricle as a pump and regulate myocardial oxygen consumption and delivery. Experiments on isolated cardiac tissue have established that myocardial fiber shortening is dependent on three factors: the preload, which determines the muscle fiber's end diastolic length; the contractile or inotropic state of the myocardium; and the afterload (ventricular systolic tension during ejection). The ventricular afterload in the intact heart is defined as the wall tension that the left ventricle must develop to eject stroke volume. According to the Laplace equation, this depends on intraventricular pressure, wall thickness, ventricular size and shape. Ventricular afterload is regulated by the impedance which is offered to the ventricle during its ejection and is chiefly determined by arterial blood pressure which in turn depends upon the peripheral vascular resistance and cardiac output. Normally there is a curvilinear relationship between the left ventricular preload (left ventricular end-diastolic volume) and its stroke work as expressed by the Frank-Starling ventricular function curve.

The cardiac output of the normal heart is principally governed by systemic venous return, with the left ventricle operating on the steep ascending limb of its function curve. Aortic impedance is of little importance. However, in the presence of left ventricular dysfunction, arterial resistance is elevated and cardiac output becomes very dependent on outflow impedance. The venous return has minimal influence with the ventricle operating at the apex of its depressed function curve (Fig). Since both preload and impedance are increased in heart failure, intramyocardial wall tension, a principal determinant of myocardial energetics, is also elevated in the failing heart, thereby increasing the cardiac oxygen requirements.[1]

In addition, the marked peripheral arterial and venous constriction in heart failure may be excessive. Thus, the systemic vascular resistance is higher than necessary and this leads to a reduction in the cardiac output. This vasoconstriction results from increased stimulation of the vascular alpha$_1$ receptors due in part to neurogenic mechanisms and high levels of circulating norepinephrine. Further, angiotension II contributes to the elevated systemic vascular resistance. The exact mechanism for the activation of the renin-angiotensin aldacterone system in heart failure is not known. However, the increased renin release is associated with increased levels of angiotensin II which increases the systemic vascular resistance. The increased aldacterone levels then lead to salt and water retention with aggravation



Relationship of stroke volume, left ventricular filling pressure, and impedance in normal and failing left ventricle. In normal heart (point N) the stroke volume is mainly regulated by changes in the preload. In heart failure (point E) stroke volume is mainly regulated by changes in impedance. In heart failure an arteriolar dilator increases stroke volume with a slight decline in left ventricular filling pressure. An arteriovenous dilator increases stroke volume and decreases LVFP. A pure venodilator reduces LVEP with little or no change in stroke volume.

Address correspondence to Dr Gould, Chief of Cardiology, Department of Medicine, The Methodist Hospital, 506 Sixth St Brooklyn, NY 11215.

of the heart failure.[2] Vasodilator therapeutic reduction of impedance and preload interrupts this deleterious sequence of events by partially counteracting the compensatory sympathetic reflex mechanism, thereby augmenting the cardiac output, diminishing pulmonary congestion, and improving myocardial energetics.

The traditional treatment of congestive heart failure involved the administration of the inotropic drug digitalis, and the concomitant administration of a diuretic. It is now recognized that digitalis can increase the systolic arterial pressure and the velocity of fiber shortening with a resultant increase in myocardial oxygen demands. This is potentially detrimental in ischemic heart disease. On the other hand, a reduction in preload with diuretic agents may produce a decline in blood pressure and hypotension, particularly in patients with an acute myocardial infarction. Further, this traditional approach to therapy may be inadequate in relieving the circulatory congestion in more severe degrees of cardiac failure.

The hemodynamic responses of the various vasodilator drugs vary. The arteriolar resistance bed may be predominately affected by some vasodilator drugs and the venous capacitance bed by others. Still other vasodilator agents possess beneficial effects on these two vascular beds. Hydralazine acts mainly on the arterial bed, the nitrates act mainly on the venous bed, while nitroprusside and prazosin have balanced actions on both beds.

Sublingual nitroglycerin has been used for 100 years in the treatment of angina. However, its use in the treatment of congestive heart failure and reduction of infarct size is relatively new. In October 1981 an intravenous nitroglycerin preparation was approved by the Food and Drug Administration (FDA). Therefore, interest in the use of this preparation has increased markedly.

The currently available commercial preparations of nitroglycerin for intravenous administration contain either 0.8 or 5 mg/mL in 5- to 10-mL ampules. These solutions are then diluted with normal saline or 5% glucose in water to a final concentration of 60 or 240 μg/mL. The solution is delivered via a special plastic administration set that does not permit significant absorption of nitroglycerin to the plastic tubing.[3] The beginning dose is 10 to 20 μg/min which is increased by 5 to 10 μg/min every five to ten minutes until the desired hemodynamic or clinical response is obtained.

The FDA has approved intravenous nitroglycerin for the management of left ventricular failure complicating myocardial infarction. Potential applications include the management of acute left ventricular failure secondary to acute mitral regurgitation or aortic insufficiency as well as acute ventricular septal rupture. The drug can also be used for the treatment of the acute exacerbation of chronic heart failure.

PHARMACOLOGY

Nitroglycerin, as well as all organic nitrates, produces dilatation of smooth muscle in blood vessel walls. Its dilating actions are maximal on the veins or capacitance vessels and least on the arteries or resistance vessels of the body.[4]

The mechanism of action of nitroglycerin is unknown. One hypothesis is that nitroglycerin and its related compounds acts on a specific nitrate receptor site in the vascular wall.[5] The active nitrate molecule reacts with a sulphydryl group at the receptor and is subsequently reduced releasing nitrite ion which initiates vascular relaxation. Depletion of available sulphydryl groups with the formation of disulfide bridges on vascular smooth muscle results in decreased responsiveness or tolerance to nitrates.[6] A more recent explanation is that nitroglycerin might induce endothelial cells to synthesize prostacyclin, a known vasodilator and inhibitor of platelet aggregation. Thus, nitroglycerin can affect the balance between the release of prostacyclin from the vascular endothelium and of thromboxane from the platelets.[7]

Nitroglycerin and organic nitrate esters are metabolized in the liver by the enzyme glutathione organic nitrate reductase to mono and dinitrol metabolites, which have no vasodilator activity.[8]

In the coronary circulation, nitroglycerin acts mainly on the large epicardial coronary arteries. The drug's vasodilating action on the small intramyocardial coronary vessels is relatively small. Nitroglycerin is a potent dilator of the pulmonary vascular bed.[9] The nitrates produce cerebral vasodilatation and may elevate the intracranial pressure.[10] The splanchnic circulation acutely vasoconstricts during nitroglycerin administration. The renal blood flow falls if the mean arterial pressure declines.[9]

Nitroglycerin is a potent vasodilator of venous vascular smooth muscle with only a modest activity as an arteriolar dilator.[4] The nitrates will therefore consistently lower the left ventricular filling pressures as well as the right heart pressures. The degree of lowering of the pressure is variable and unpredictable. However, vasodilators in general are more effective when the calculated systemic vascular resistance is elevated. Patients with the highest pulmonary wedge pressures have the best clinical response, often showing an increase in the stroke volume and cardiac output. Subjects with borderline elevated or normal left ventricular filling pressures typically respond with a significant decrease in the stroke volume.[11] The nitrates are beneficial for individuals with major elevations of left ventricular filling pressure. It has been shown that when the wedge pressure is greater than 15 mm Hg the nitrates may increase the stroke volume through arteriolar dilatation and impedance reduction.[12]

Hemodynamic measurements are extremely important when administering intravenous nitroglycerin, particularly in patients with an acute myocardial infarction. Usually the blood pressure can be monitored by cuff measurements.

ACUTE LEFT VENTRICULAR FAILURE IN MYOCARDIAL INFARCTION

Vasodilator therapy has been shown to improve ventricular function in patients with left ventricular failure complicating acute myocardial infarction. After coronary occlusion in the experimental animal, nitroglycerin has been shown to reduce ST segment elevation and infarct size, improve ventricular function, raise ventricular fibrillation threshold, and enhance electrical stability of the heart by decreasing differences in refractory periods between ischemic and nonischemic zones.[13] Sublingual nitroglycerin,[14] oral nitrates,[15] and nitroglycerin ointment[16] have been shown to produce beneficial hemodynamic effects in patients with an acute myocardial infarction.

Intravenous nitroglycerin has been administered to patients with an acute myocardial infarction. Kötter and his co-workers[17] administered the drug to 12 patients and lowered the mean systemic arterial pressure to 80 mm Hg. A significant reduction in the left ventricular filling pressure was observed. However, there was also a significant decrease in the stroke volume and cardiac index. The authors stressed that the decline in the cardiac index was not dependent upon the initial filling pressure. Flaherty and his group[18] administered intravenous nitroglycerin to 12 patients with an acute myocardial infarction. They also observed a decrease in the left ventricular filling pressure with no significant change in the stroke index or cardiac index. In a subsequent study, Flaherty and his co-workers[19] administered a higher dose of intravenous nitroglycerin to patients with an acute myocardial infarction. In the patients with the most severe left ventricular dysfunction, a reduction in the left ventricular filling pressure was associated with no change in the cardiac index. They also observed a significant reduction in the ST segment elevations during the nitroglycerin infusion. However, the use of intravenous nitroglycerin for infarct size reduction must be considered experimental.

Gold and his group[14] administered sublingual nitroglycerin to patients one week after their myocardial infarction. The cardiac output rose in patients with moderate or severe left ventricular failure while it fell in patients without left ventricular failure. Recently Rabinowitz and his group[20] administered intravenous isosorbide dinitrate to 18 patients with heart failure due to an acute myocardial infarction. Isosorbide dinitrate markedly decreased the pulmonary capillary wedge pressure, modestly increased the cardiac output, and decreased the systemic vascular resistance. Four patients in their study did not improve hemodynamically. These four patients had a low to normal systemic vascular resistance of less than 1,500 dyne-sec-cm^{-5}. This suggests that patients with low to normal systemic vascular resistances are poor responders to therapy as compared to those with elevated systemic vascular resistances.

It appears inescapable that careful monitoring of the pulmonary and systemic arterial pressure is required when administering intravenous nitroglycerin to patients with an acute myocardial infarction.

In patients with right ventricular myocardial infarction, associated with an inferior wall myocardial infarction, nitroglycerin might be harmful. An increased right-sided filling pressure is important to maintain the cardiac output. Nitroglycerin, which reduces the right-sided venous return, will decrease the cardiac output and this can lead to hemodynamic deterioration.

CONGESTIVE HEART FAILURE

Intravenous nitroglycerin can produce beneficial hemodynamic and clinical effects in patients in heart failure due to an acute myocardial infarction. This has been documented in a number of scientific reports.[18,19] Intravenous nitroglycerin would also appear to play a role in the management of acute mitral regurgitation and acute ventricular septal rupture complicating acute myocardial infarction. A reduction in left ventricular afterload should decrease the degree of mitral regurgitation and also reduce the magnitude of the left to right shunt. Recently Esente and his co-workers[21] administered intravenous nitroglycerin to eight patients with severe mitral regurgitation, chronic in four and acute in four cases. All of the patients in this group exhibited a pulmonary artery wedge V wave of 50 mm Hg or greater. After nitroglycerin injection, a 50% or greater reduction of V wave amplitude was observed in all patients. A dramatic reduction in the left ventricular end diastolic pressure was also observed. Nitroprusside has also been reported to produce this hemodynamic improvement in patients with mitral regurgitation.[22] However nitroglycerin has a major advantage over nitroprusside. Nitroglycerin can dilate the intercoronary collateral vessels while nitroprusside's effects on these vessels is variable. At times nitroprusside may even produce a coronary artery steal.[23]

Intravenous nitroglycerin can be administered to patients in chronic congestive heart failure. Pitt and his group[24] studied ten patients in chronic congestive heart failure. They administered nitroglycerin at a mean infusion rate of 0.6125 μg/kg/min. A significant decline in the mean arterial blood pressure, mean pulmonary artery pressure, mean pulmonary artery wedge pressure, and heart rate were observed. The cardiac output showed a small nonsignificant decline.

Rabinowitz and his group[20] administered intravenous isosorbide dinitrate to 22 patients with chronic refractory heart failure. Fifteen patients had coronary artery disease; four, congestive cardiomyopathy; and three, rheumatic mitral insufficiency. Intravenous isosorbide dinitrate markedly reduced the filling pressures and also produced a moderate increase in the cardiac output. The patients with mitral insufficiency also responded in a similar beneficial manner to the drug infusion.

It must be remembered that intravenous nitroglycerin has only limited and temporary efficacy. The effectiveness of this agent is dissipated rapidly with time. Flaherty and his co-workers[18] observed that 30 minutes after the cessation of a nitroglycerin infusion, the hemodynamic parameters had almost returned to baseline values.

SIDE EFFECTS

Intravenous nitroglycerin is well tolerated. Hypotension, sinus tachycardia, and sinus bradycardia can occur with a sudden reduction in the blood pressure. Headache is one of the complications of nitroglycerin therapy. In fact, nitroglycerin should not be administered to patients with elevated intracranial pressure, since venodilatation can cause a further increase in intracranial pressure.[3]

A metabolic hazard may also exist. For each mole of nitroglycerin metabolized, one mole of nitrite (NO_2–) is formed. Hemoglobin oxidation to methemoglobin may occur in significant quantities, especially in the presence of methemoglobin reductase deficiencies or in congenital M hemoglobin variants.[25] However, this is a rare complication.

A decrease in arterial oxygen tension, associated with an increase in the alveolar-arterial PO_2 gradient and a rise in venous admixture, have been observed in patients receiving nitroglycerin.[26] The reduction of PaO_2 following nitroglycerin probably results from ventilation-perfusion mismatch.

CONCLUSION

Intravenous nitroglycerin is an important medical treatment for acute and chronic heart failure. Initially, vasodilators were used only when digitalis and diuretics could not adequately treat congestive heart failure. Now many clinicians view vasodilator drugs as equal or better alternatives than digitalis and diuretic agents. Vasodilator therapy is one of the major advances in the treatment of heart failure.

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Health professionals work for sexual rights of disabled persons

A decision by the United States Supreme Court on the constitutionality of a New York State law that could be used to prosecute consenting adults for acts of sodomy may restrict the information health care professionals can discuss with their disabled patients. The law forbids loitering for the purpose of soliciting for "deviant" sexual intercourse, such as sodomy.

The dispute over the law also highlights both the physical and social problems that people with disabilities face when dealing with the issue of their right to engage in sexual activity. For those with physical disabilities, the variety of sexual activity may be restricted because of a limited range of movement. Health care professionals who counsel such patients often advise them on ways to achieve sexual satisfaction despite these limits. Such advice may include recommending that the person explore whatever sexual alternatives are physically possible, including oral sex.

The court heard arguments on the case on January 14, but will not render an opinion until after its docket is cleared, which may occur as late as July.

Barbara Whitney, RN, director of the Manhattan-based Sex Information and Education Council of the United States (SIECUS), told the *Journal* that the law can be interpreted as a far-reaching prohibition of private acts of sodomy between consenting adults. The New York State Court of Appeals had declared in 1980 that consensual sodomy is not a criminal act. Since the object of the loitering statute is specifically to punish such conduct, the court declared it unconstitutional. The state appealed

Marian Dunn, PhD, co-director of the Center for Human Sexuality at Downstate Medical Center, teaches disabled persons how to enjoy their sexuality despite their physical limitations.

News Features is compiled and written by Marc Kusinitz, PhD.

> *"Even the educational material that we use would become illegal."*

that ruling, and last October the Supreme Court agreed to review the appeals court's decision.

Two other organizations cooperated with SIECUS in filing the brief: the Society for the Scientific Study of Sex, an interdisciplinary society of professional sex researchers and clinicians that publishes the *Journal of Sex Research*, and the Coalition of Sexuality and Disability (CSD), a Manhattan-based organization that provides information on sexual health care services for people with disabilities. The brief supported the right of sexual privacy of consenting adults and pointed out that the law would be especially unfair to those people who are physically disabled.

MEDICAL INFORMATION GAP

A law that appears to discriminate against disabled persons is an example of the difficulties of the handicapped in asserting their sexual rights. The problem is particularly acute in the health care setting. Several individuals in this field told the *Journal* that the problem is due in part to the general lack of training of physicians in the sexual problems of the disabled and to the reluctance of many physicians and sex therapists to discuss the issue with their disabled patients.

Ms Whitney said that in helping to file the brief SIECUS was representing the right of everyone to sexual privacy.

"The obstacles many disabled persons must overcome in order to achieve sexual satisfaction made the law especially unfair to them," she added. "We felt that some people with disabilities would be discriminated against if certain forms of sexual conduct were made illegal. Also, as professionals, it would make it criminal for us to counsel anybody on the wide range of sexual behavior. Even the educational material that we use would become illegal."

Although courses on sexuality are taught in most medical schools, the topic of disability and sexuality is often omitted. Daniel Goldberg, PHD, Director of the Center for Human Sexuality at Jefferson Medical College in Philadelphia, told the *Journal* that the subject of disability and sexuality "has a long way to go. I don't think medical education covers this very well."

The lack of such training in medical schools was also cited as a problem by Richard Cross, MD, a professor in the Department of Environmental and Community Medicine at the University of Medicine and Dentistry of New Jersey, Rutgers Medical School. But he said that medical school is really not the place to cover that subject. The emphasis is not on trying to make second year medical students competent to deal with practical problems they encounter, but to make them aware of the problem.

In addition to the paucity of formal courses, there is the problem of defining the word "disability." When asked what the word meant in the context of this issue, Anne Berkman, a sex counselor at both the Manhattan and Bronx Veterans Administration Hospitals, explained that there are physical, emotional, mental, and sexual disabilities. In fact, she said, the majority of those people with sexual dysfunction are not emotionally, mentally, or otherwise physically disabled. Ms Whitney pointed out that a large but unknown percentage of the millions of people on hypertensive medication suffer from sexual dysfunction caused by the medication, most often impotence in men and lack of arousal and lubrication in women. She also said that 50% of the country's 11 million sufferers from diabetes mellitus have sexual dysfunction related to impaired blood circulation. A recent review article on sexual dysfunction in males with diabetes pointed out that impotence is between two and five times more common in diabetic men than in nondiabetic men (*NY State J Med* 1983; 83:1174-1179).

The term "disability" itself can be misleading. As an example, Ms Whitney pointed out that the person who has polio and is confined to a wheelchair may have no sexual dysfunction. On the other hand, she emphasized that there are emotional and social aspects to disability that can affect a person's sexual activity.

"Those of us in the field feel very strongly about the use of 'sexuality' as meaning the total person and all that you are," she said, "including pride in one's gender and the social and psychological implications that disability and dysfunction bring with it."

NOBODY HAS TIME

Ms Whitney said that these feelings affect a person's way of forming relationships and feeling good about them, and are an important aspect of sexuality. But according to Ms Berkman, it is difficult to interest physicians in engaging their patients in discussions of their sexual concerns.

"But then, I'm working in a very busy place (the VA hospital setting) where nobody has time. And that's the quote: 'Nobody has the time.' And the other quote is: 'It's not my job.' It's nobody's job when you think about it. That's why a few of us have taken responsibility."

Ms Berkman said that, because physicians don't go to programs unless they are medically oriented, having trained counselors on hospital staffs is of limited help in educating the medical community to the sexual needs of the handicapped.

The Institute of Rehabilitation Medicine at New York University Medical Center offers seminars for both professionals (who make up about 60% of the attendees) and patients, according to Frank Padrone, PHD, a clinical assistant professor in rehabilitation medicine at the institute. These seminars, called Sexual Attitude Reassessment (SAR), help both health professionals and patients understand the sexual problems faced by disabled persons, and serve as a guide to dealing with these problems. The institute's SAR was modeled on one established at the University of Minnesota, and brought to NYU in 1973 by Dr Padrone.

At Rutgers, Dr Cross holds group therapy sessions for disabled patients. These sessions include films that show disabled persons involved in various activities. They show not just sexual techniques, but also the entire relationship between people, touching on everyday problems of the handicapped.

A highlight of the Rutgers group sessions is Harilyn Rousso's talk. Ms Rousso, who suffers from cerebral palsy, is a psychotherapist who teaches at Rutgers as well as at schools around the country. She talks to the group about her personal sexual experiences growing up, and what it is like to go through adolescence with her disability. She describes

"Physicians don't attend programs unless they are really medically oriented . . ."

the difficulty her parents and other people had in accepting the fact that she had sexual feelings. "She's a very eloquent teacher," Dr Cross said, "and has the audience close to tears as she describes what she went through."

Ms Rousso, who has a private practice in New York City, told the *Journal* that about half of her practice is with men and women with physical disabilities. She is particularly interested in women, because "they face a double stereotype. Women face second class status in our society," she said, "and disabled people face second class status. So if you're a woman, you have the worst of both worlds."

Ms Rousso said that by including sexual issues in the treatment of people with disabilities as part of the overall treatment of that individual, "it becomes a more natural weaving of that into your work." She pointed out that changing one's attitude toward the issue is the most important place to start.

"It ought to start with the realization that disabled people are sexual—that if you're going to work with them, you're going to have to include their sexuality in your treatment of them. So you have to both listen to the cues of their own curiosity and concern about their sexuality, or, if you don't hear them questioning or being curious, you have to raise the issue yourself in a very direct way."

DENYING SEXUAL FEELINGS

The reluctance of some people with disabilities to assert themselves sexually is due, at least in part, to the feeling that they are not entitled to sexual activity, according to Marian Dunn, PhD, codirector of the Center for Human Sexuality at Downstate Medical Center in Brooklyn.

"Everything conspires to make them feel that way," she said. She cited the example of married couples, both members of which are handicapped and require home health aides to bathe, dress, and undress them, and put them to bed. "Just imagine what your sex life would be like if you were dependent on outside people," she said. Dr Dunn explained that some health aides feel that the people they care for are not entitled to be sexual.

The situation of young, unmarried disabled people can be even worse. Having to arrange for transportation as well as for privacy with a date can be almost insurmountable obstacles to the fulfillment of their social lives. In addition, Dr Dunn said, there are psychological obstacles to dealing with the myth that people who are disabled are not entitled to be sexual, and "the lousy body image that you grow up with when you're handicapped or when you develop some kind of handicap later in life that distorts your body image."

Sometimes, the feelings of lack of entitlement among young people who are disabled are provoked by the insensitivity of those charged with their care.

"If our society gives you the feeling repeatedly that you're not a sexual being because you're not physically perfect—and remember, ours is a society that emphasizes physical beauty—then you grow up feeling as if this is not for you," said Dr Dunn.

PROFESSIONALS FEEL VULNERABLE

Dr Padrone said that disabled persons may lack a feeling of entitlement because of feelings of inadequacy, and fears that they cannot give of themselves or perform well sexually. These people feel that they cannot expect much in return and lose the feeling that they're entitled to sex.

Dr Dunn suggests that "When we're dealing with someone who's handicapped, it's scary. It makes us feel vulnerable all of a sudden and concerned about all the things that can go wrong with our body. So dealing with sexuality is even scarier. How would I look under those limitations? How would I feel about my body if it was twisted or I couldn't move limbs or I couldn't speak clearly? So it's off-putting for the health care professional."

Dr Padrone also cited both lack of training in medical school as well as personal, emotional feelings on the part of physicians, as contributing to the problem. He pointed out that, since most of the physicians in the US have been brought up in this country, they are "saddled with the same kinds of feelings of anxiety, discomfort, and taboos that all the rest of us are." Rather than reflecting a failing on any physician's part, he said that it's "simply reflecting the state of society."

DISABLED AREN'T DIFFERENT

Another obstacle in the way of some disabled persons, according to Dr Dunn, is the fact that Medicaid and Medicare do not pay for sex counseling, and clinics like hers cannot extend themselves as much as they would like without more funding. "We're part of an institution," Dr Dunn said, "but we have to pay our own way."

Although such institutions must provide some specialized sexual counseling for disabled patients, in general, according to Dr Dunn, "the work is not terribly different than working with able-bodied clients." One difference is that therapists from the clinic may make home visits to learn how a disabled couple's house is set up and what restrictions there are in terms of their movement and accessibility to each other.

The fact that the concept of sexuality is even an issue reflects the alienation of many people with disabilities. Films depicting the daily routine of handicapped individuals, such as those that Dr Cross shows, also emphasize this alienation, as well as the accommodations disabled people must make in even the most routine circumstances. Yet the effect of such films is more than an appreciation by the viewer for the obstacles disabled people must overcome. According to Dr Cross, showing the interaction of two handicapped persons of the opposite sex as they talk, argue, or embrace "does bring home the fact that the disabled are human beings."

For more information, contact:

Trish North
Coalition on Sexuality and Disability
122 E 23rd Street
New York, NY 10010
(212) 677-7400

Barbara Whitney, RN
Sex Information and Education Council of the US
80 Fifth Avenue
New York, NY 10010
(212) 929-2300

Professional "companions" for rape victims

Victims of rape in Suffolk County can receive support from a hospital "companion" trained in crisis intervention, and hospital, police, and legal procedures. The companion service, set up to help the victim during the first few hours following a sexual assault, is run by the Victims Information Bureau of Suffolk (VIBS). About 20 volunteers, who have gone through the Bureau's 22-hour training program, are on call at hospitals to assist victims. Hospitals will call for a companion if a victim requests one, but the policy at University Hospital at Stony Brook and Brookhaven Hospital is to call a companion automatically. Although victims will not be pressured by companions to report a rape to police, VIBS hopes that the service will encourage women to do so, according to Martha Wray, head of the nonprofit counseling service. Information on the counseling service can be obtained by calling (516) 360-3606.

Delivering drugs by means of red blood cells

The United States Department of Agriculture (USDA) has developed and patented a technique for ensuring the slow release of drugs into the bloodstream by means of encapsulation inside red blood cells that act as time-release capsules.

Researchers at USDA's Agricultural Research Service in Kerrville, TX, and at the Veterinary Toxicology and Entomology Laboratory, College Station, TX, encapsulated a short-lived cancer drug called cytarabine inside canine blood cells. The encapsulated cytarabine maintained a therapeutic level for 10 days when injected into the animal, as opposed to two hours after conventional injection of the drug.

To encapsulate drugs, red blood cells are first placed into a dialysis bag, where they swell until microscopic pores develop in their membranes. The blood cells are then removed from the bag, mixed with a drug, and exposed to a salt solution that causes the cells to shrink back to their normal size. The pores close during the shrinking process, trapping the drug within the cell.

According to USDA scientists, the technique may eliminate the need for high doses of drugs to be administered at frequent intervals. The USDA is now working out the details of licensing the patents to industry.

Transplant service matches bone marrow donors and recipients

The American Association of Blood Banks (AABB) has set up a free bone marrow transplantation information service to facilitate contact between transplant centers needing donors of a specific HLA (human leukocyte antigen) type and blood donation centers that have access to donors who have already been HLA typed.

The system protects the privacy of donors and recipients, while eliminating the expense and red tape of a separate agency. The AABB compiles requests from transplantation centers for donors of particular HLA types and distributes them at regular intervals (monthly, or more regularly, if warranted) to donor centers having HLA-typed registries. If a match between a transplant center and a donor center occurs, the donor center will contact and negotiate directly with the transplant center.

For more information write to the following address:

Bone Marrow Transplantation
AABB
1117 N 19th Street
Suite 600
Arlington, VA 22209

Nation's legislatures to consider hundreds of health cost bills in 1984

According to the findings of a study entitled *Major Health Issues for the States: 1984*, the 43 state legislatures holding sessions this year will consider a total of more than 400 bills aimed at controlling health care costs. Among the findings of the study, which was done by the National Conference of State Legislatures (NCSL), is that the states will introduce 140 bills dealing with Medicaid, 34 bills dealing with hospital regulation, 51 bills concerning nursing homes and alternatives to long-term care, and 76 bills dealing with health insurance.

The NCSL represents the nation's 7,438 state legislators and their staffs. Its role is to improve the effectiveness of state legislatures, promote interstate communication and cooperation, and assure strong state input into federal decision making.

The NCSL study was published under a grant from the Health Care Financing Administration, and copies can be obtained for $10.00 prepaid by writing to the following address:

Chris Tracy
National Conference of State Legislatures
1125 17th Street
Suite 1500
Denver, CO 80202

NEWS BRIEFS is compiled and written by Marc Kusinitz, PHD.

A SHORT TEXTBOOK OF MEDICINE

Seventh edition. By J. C. Houston, MD, C. L. Joiner, MD and J. R. Trounce, MD. 772 pp., illustrated. New York, Arco Publishing, Inc., 1983. $19.95.

This is the seventh edition of a book, originally published 20 years ago, attempting to present current and concise data in an inexpensive volume that can be readily replaced every few years. It is British in its background and approach, at times mentioning medications that are not available in the United States, and at other times mentioning medications specifically by brand name. The book moralizes in regard to diseases like alcoholism and obesity. For instance, "Human beings have an enormous capacity for damaging themselves in the pursuits of pleasure, whether through alcohol, drugs, riding fast motorcycles, or smoking heavily." And, obesity "is a serious disease common in prosperous communities . . . The common cause accounting for 90% of this hyperphagia is gluttony." Many readers will be put off by this approach.

It is interesting to note, however, that the difficulty in maintaining intake and output records of patients in Great Britain is as great as in the United States. In the chapter on fluid and electrolyte balance, disorders are more accurately followed by serologic and urologic testing and clinical signs and symptoms.

The book's major asset is its readability. It is suitable as a "refresher" in medicine, but it is too superficial in some areas. For example, there is no chapter on oncology and the hematology chapter is brief. A new chapter on tropical diseases is of interest but of little practical use. The chapter on neurology is so good as to impress even a neurologist. In a departure from usual texts, there are two chapters, one on steroids and the other on antibiotics, that discuss these medications specifically and in a unique, useful, and practical way. The tables summarizing new findings in immunology are excellent and should be kept for easy reference in the physician's office.

The chapters and the bibliography for each chapter vary in quality. Paradoxically, the acid-base chapter has as its most recent reference a 13-year-old article, but it is an excellent review. It is not necessary to have taken a recent course in biochemistry or physiology to understand the problems presented. The cardiology section is inconsistent. Acute rheumatic fever receives a great deal of attention; pulmonary thromboembolism gets very little coverage. Thallium scanning and technetium scanning are explained, both in regard to diagnosis and usefulness, in terms of evaluating coronary artery perfusion and left ventricular muscle function. There is little in the chapter regarding cardiopulmonary resuscitation and barely a mention of the calcium channel blocking agents. In the respiratory disease section, asthma is superbly covered, while pulmonary fibrosis is hardly mentioned. The introduction to this section has an excellent discussion on the physical diagnosis of the chest. But should this be in a "short" medical text?

In conclusion, although this book does not make for leisurely bedtime reading, it is a more enjoyable way of reviewing medicine than either studying a two-volume standard textbook or simply reviewing the bare outline of topics for board recertification.

PHILIP P. BONANNI, MD
The University of Rochester
Medical Center
Rochester, NY 14642

HERPES: THE FACTS

By J. K. Oates, MD, 123 pp., illustrated. New York, Penguin Books, 1983. $3.95.

As the number of cases of genital herpes infections has continued to increase, the media has created significant hysteria among both patients and the sexually active. Physicians caring for these patients have frequently been frustrated by their attempts to provide adequate treatment and appropriate emotional support. The author, Dr J. K. Oates, a distinguished clinician in the field of Genito-Urinary Medicine, has recognized this dilemma and dealt with it successfully.

His book is an outgrowth of his own attempts to put this important disease into proper perspective for patients. He begins with a historical discussion of herpes infections and follows with basic information on various viral diseases and laboratory methods with specific emphasis on herpes. His descriptions of herpes infections include not only the clinical syndrome in men and women, but also the methods of infection and the body's defense mechanisms. The discussion of immune mechanisms, which could have been very complex, is easy to understand. The sections on prevention and treatment are very fair and well balanced. Two potentially controversial topics, the relationship of cervical cancer to herpes and the management of pregnancy in patients with herpes, are treated with great sensitivity. The section on special problems deals with neonatal herpes, herpes encephalitis, herpes in the immunosuppressed patient and sexual function. The last chapter, which contains questions and answers, is primarily used to reemphasize the points that the author thinks are most important. This technique is very effective.

This small book contains authoritative, accurate information clearly and concisely expressed. The material is presented in a sensitive and easily readable style that will be very reassuring and supportive to patients without appearing to be condescending. This is an extremely valuable reference for all physicians to recommend to their patients suffering from genital herpes infection. It is considerably better than other available sources of information.

LEWIS M. DRUSIN, MD
The New York Hospital-
Cornell Medical Center
New York City 10021

THE AIDS EPIDEMIC

Edited by Kevin M. Cahill, MD, 173 pp. New York, St. Martin's Press, 1983. $12.95 (hardcover), $7.95 (softcover).

THE ACQUIRED IMMUNE DEFICIENCY SYNDROME AND INFECTIONS OF HOMOSEXUAL MEN

Edited by Pearl Ma, PhD and Donald Armstrong, MD, 442 pp. New York, Yorke Medical Books, 1983, $39.50 (hardcover).

AIDS: THE MEDICAL MYSTERY

By Frederick P. Siegal, MD and Marta Siegal, MA, 269 pp. 1983. $19.50 (hardcover), $7.95 (softcover).

The Acquired Immune Deficiency Syndrome (AIDS) is a disease of low morbidity but of extremely high mortality (41% of the 3,210 known cases had died by late January, 1984). Since 1981, when AIDS cases were first regularly reported, approximately 1,000 cases have been documented per year in the United States. During the same period as many cases of chancroid and of Rocky Mountain Spotted Fever have been reported each year in the United States. Thus AIDS is, from any perspective, an extremely rare disease at the present time.

Daily coverage of the disease in the press and media elevated AIDS to sensational levels that reached a fever pitch in the summer of 1983. As a media event, AIDS was following in the footsteps of Swine Flu and Legionnaires' Disease, both of which have long since been relegated to backburner interest by the press and media.

Despite explicit and implicit press and media projections earlier in 1983, that AIDS was about to run rampant, the disease's prevalence has in fact leveled off. This is particularly significant in view of the fact that an extensive active surveillance system exists at present for ferreting out every possible case. Whether or not this trend will continue is unknown.

The AIDS Epidemic essentially presents the proceedings of a scientific symposium held on April 10, 1983, sponsored by the Tropical Disease Center of Lenox Hill Hospital and the publisher, St. Martin's Press (according to promotional material furnished by the publisher). The symposium brought together public health officials and medical scientists who have been in the forefront of the research and surveillance programs for AIDS. Thus much of the book's content reflects the most authoritative views on AIDS as of the spring of 1983. Much has happened since that time. The corpus of scientific information about the epidemiology and clinical manifestations of the syndrome has been greatly enlarged, rendering some of the book's content dated.

The book was physically designed and marketed for mass appeal to the lay public. One could argue that this is an attempt to reach out to high risk groups with helpful information. Unfortunately, various segments of the book are very technical, as would be expected since they were part of a medical symposium. Few nonmedically trained individuals who purchase this book will be able to comprehend most of it. However, physicians will find its content of great interest and extremely useful.

Some readers will be troubled by the editor's preface, entitled, "The Evolution of An Epidemic." Identical to his *New York Times* Op-Ed editorial entitled "Conquering AIDS," published on April 22nd, 1983, it attempts to make a case for alleged government inaction contrasted to the editor's own claimed courage in dealing with the disease through steady, loyal service to patients. In point of fact, the book's contents are the strongest refutation to these allegations. They chronicle in great detail most of what was done by government and private researchers as early as June 1981, before the editor was speaking out on AIDS. In 1983, Edward N. Brandt, Jr, MD, Assistant Secretary for Health of the U.S. Department of Health and Human Services fully described the expenditures of Federal agencies on AIDS research. In 1982, $5.5 million was spent on AIDS-related work and in 1983, $14.5 million. This scarcely supports the editor's allegations of governmental inaction.

The AIDS Epidemic will principally be of interest to physicians. It presents much useful information, concerning virtually all aspects of the disease, in a concise manner. As would be expected in a multiple author text, there is considerable unevenness in the quality of the writing and some evidence of hasty editing. The book, however, is well organized and can be read as a cohesive whole from cover to cover. It contains a moving invocation by the late Terence Cardinal Cook.

The Acquired Immune Deficiency Syndrome And Infections of Homosexual Men is a multi-authored book (57 contributors), the first third of which (149 pages) deals with sexually transmitted diseases among homosexual men. Many of the contributors to both this section and the one on AIDS have published a great deal on their respective topics in the recent past. A cross check of some published material revealed not only similarity but identical passages in certain instances. Some, no doubt, would argue that bringing together even warmed-over prior publications dealing with the same subject is useful. And this is often done in books that present reprints from the medical literature. But there is a difference here in that the contents of this book are not represented as reprints.

The first third of the book is divided into three parts, each containing several chapters. These parts include Sexually Transmitted Diseases—Non-Diarrheal, Sexually Transmitted Diseases—Diarrheal and Other Sexually Transmitted Diseases. The remaining sections primarily deal with AIDS. They are Infections and Neoplastic Complications of AIDS, Immunologic Evaluation, Methods and Controls, and Diagnostic Perspective.

As a scientific update on AIDS, this book leaves few areas untouched, covering almost every aspect of the syndrome in considerable detail. Significantly, the AIDS problem among Haitians is glossed over as part of a brief four-and-a-half page overview of the epidemiology of AIDS in the United States. Some readers will recall that in the summer of 1983, the New York City Department of Health removed Haitians from the high-risk category following intense national political pressure from Haitian groups.

It is noteworthy that this book, edited by two New York City based medical scientists and prefaced by the Commissioner of the New York City Department of Health, scarcely mentions Haitians and their relationship to AIDS. In contrast, *The AIDS Epidemic* has a 10-page chapter entitled, "The Haitian Connection." Its author, Sheldon H. Landesman, MD, presents a candid overview of the AIDS problem among Haitians, while simultaneously admitting that there are many unanswered questions on the subject.

The Siegals, in their book *AIDS: The Medical Mystery*, provide a comprehensive overview of the subject, detailing not only the scientific facts, but also the political and economic reasons why Haitians would not want to be stigmatized as being an AIDS high-risk group. As the Siegals point out, the attack rate among Haitians in the US is 102 per million, 10-fold that found in Americans and is comparable to the 124 per million found among American homosexual males. One could cogently argue, however, that attack rates among certain other third world populations might be found to be just as high were they studied as intensively as the Haitians have been. It is reasonable to conclude that the AIDS problem among Haitians and other third world populations remains ill defined in an epidemiologic sense at this point in time. Therefore present arguments over whether or not Haitians are a high-risk group are in a sense engagements in sterile polemics.

The Ma and Armstrong book is well organized, but not structured to be read from cover to cover. Unlike the Cahill book, whose concise 13 chapters can be read in one sitting, the 29 chapters of this book are so diverse and detailed, that readers will find it more useful as a reference volume.

AIDS: The Medical Mystery is a book intended for the general public. Authored by an immunologist who has been extensively involved in the AIDS problem, it meets a need not really addressed by the other two books. Divided into eight chapters, it covers the nature of AIDS, describes the epidemic, puts forth hypotheses, speculations and predictions, discusses the medical care of AIDS patients and elaborates on preventive measures and current research directions.

The opening chapter is the story of Joey, a young man dying of AIDS. Intended to "grab" the reader, it is overly melodramatic and out of step with the rest of the book. In it, the Siegals lapse into unnecessary self-praise, occasional outbursts of which occur in subsequent chapters.

Overall the book is concise, easy to follow and authoritative. Physicians who are not very familiar with AIDS will also find it an extremely useful volume. Readers, however, should be alert to the Siegals' tendency to proclaim their own intuitions about a number of unanswered issues concerning AIDS without mustering convincing scientific evidence. Their hunches may well turn out to be correct, but at this point in time they are unsupported by scientific facts.

A third of the book consists of appendices. These are I: New York State AIDS Bill; II: Selected Testimony to New York State Senate and U.S. Congress; III: Health Resources: Clinics, Hot Lines and Referral Centers; and IV: Selected Extracts from *MMWR*. The latter covers 48 pages. Appendix III clearly has usefulness for those most concerned about their personal risk from AIDS. But the remaining appendices are of very limited interest to the general reader and represent unnecessary padding.

These caveats aside, *AIDS: The Medical Mystery* is a fine book for the layman and a good introduction to the subject for the physician.

PASCAL JAMES IMPERATO, MD
Deputy Editor

HOW TO WRITE AND PUBLISH A SCIENTIFIC PAPER

By Robert A. Day. Second edition. 181 pp., illustrated. Philadelphia, PA, ISI Press, 1983. $17.95.

Uncritical reviews of the first edition of Robert Day's book on the scientific paper, such as appeared in *The New England Journal of Medicine*,[1] were surprising because the book's content, when accurate, is not original; its sources are poorly documented; and its prose is hardly distinguished. Unfortunately, these flaws remain in the overpriced second edition, notwithstanding the author's statement in the Preface that he has corrected "the (few) [sic] imperfections that appeared in the First Edition." Justification for a new book is its display of some point of originality—in concept, substance, or style of presentation. This book can claim none of these, the previous publications of others having covered the subject more comprehensively, reliably, and eloquently.[2-5]

Day appears to have tried to fend off criticism of his insouciance toward attribution by acknowledging that he may have " 'borrowed' intact from other sources," but since the passage of time had dulled his memory, he could only beg the indulgence of his involuntary "joint authors." Since these sources are largely still in print, a gallimaufry of bits and pieces from them is difficult to justify. Moreover, is it not improper for one who purports to give scientific authors advice not to record his own bibliographic sources punctiliously? Are scientific authors to follow his suit and violate a cardinal ethical principle of scientific exposition and scholarship? In his first edition (1979), much of the "Guidelines for Reviewers" was reproduced verbatim as it appeared in the copyrighted *The Scientific Journal: Editorial Policies and Practices* (1976)[6]; yet no footnote acknowledged that source. The rearrangement of that material in the second edition does not relieve the author's obligation to cite the copyrighted source, especially when he maintained that he had done "a reasonable job" of citing references. Does Day understand his own words when he writes ". . . to use the work of others without appropriate attribution, is the type of breach in scientific ethics that is regarded as unforgivable by one's peers"? Or did he mechanically transfer previously expressed words and ideas to these pages?

Beginning with the first page and ending with the last, this book contains too many misstatements, deficiencies, and solecisms to be considered a dependable guide for scientific authors. From page one, paragraph one: "A scientific paper is a written and published report describing original research results." Not a precise, or even accurate, definition. A scientific paper (if one is to use such a loose label) is not, by definition, "published"; it may be orally presented and never published. And although a review article does not describe "original research results," Day devoted an entire chapter in the book to "How to Write a Review Paper." From page one, paragraph two: "To properly define 'scientific paper,' we must define the mechanism that creates a scientific paper, namely, valid publication." What does that *mean*? Is valid publication the mechanism that *creates* a scientific paper? Presumably, some articles are *invalidly* published, for later we read that: "When a scientific paper has been validly published in a primary journal, it thereby becomes knowledge." One would be hard put to substantiate that statement, since some material published is not even sound or accurate, let alone understood or absorbed as "knowledge." Such carelessly conceived statements and loose terminology pervade the book and represent a superficial, window-shopper's view of scientific writing rather than sound advice from a critical scholar.

Coherence is no more in evidence at the end of the book, where a series of "therefores" signifies a kind of rigorous reasoning that is patently absent: "What I have said in this book is this: Scientific research is not complete until the results have been published. Therefore, a scientific paper is an *essential* part of the research process. Therefore, the writing of an accurate, understandable paper is just as important as the research itself.

Therefore, the words in the paper should be weighed as carefully as the reagents in the laboratory. Therefore, the scientist must know how to use words. Therefore, the education of a scientist is not complete until the ability to publish has been established." Aside from its wordiness and its awkward rhetorical use of repetition, that passage, while containing some trite truths, also includes egregious nonsequiturs. The leap from the penultimate sentence to the last is especially difficult to negotiate. To state that the ability to publish completes the education of a scientist is manifestly absurd. The education of a scientist, or of anyone else, is never "complete."

Imprecision, cursoriness, and oversimplification abound. For example: "Whenever you quote or discuss previously published work, you should use the present tense; you are quoting established knowledge." And: "Your own present work must be referred to in the *past* tense. Your work is not presumed to be established knowledge until *after* it has been published." And: "Most of the Abstract should be in the past tense, [sic] because you are referring to your own present results." The principles governing proper verb tense have no such simplistic basis. Publication does not "establish" knowledge. And much that is scientifically invalid and even fraudulent is published.[7]

Wit and humor can enliven literary style when they are applied by a skilled professional writer, but in the hands of novices, they can be obtrusive and palling. After Day's lengthy relating of an exhausted joke, his "All seriousness aside" hardly amuses readers. And they are vexed, not charmed, by: "Apropos of nothing, I would mention that English is a strange language"—a statement that characterizes the patchwork quality of this book. Under "The Ten Commandments of Good Speaking" and "The Ten Commandments of Good Writing," where the reader properly expects to find positive criteria, only spoofing appears, including broadly circulated,[8] and now hackneyed, negative edicts presented as original ideas. When jokes and examples are staler than last night's beer, they fall equally as flat. One person's humor is another person's corn. And there is a vast difference between an appealing style and a self-consciously folksy one.

A book that purports to advise readers how to write well should, itself, be a model of good prose. This one is not. Day's repeated violation of rules that he prescribes implies a lack of writing experience and little comprehension of the underlying principles. On the same page on which he advocates use of the active voice, he opts for the inept passive: "This 'plural' problem was commented upon by Sir Ashley Miles . . . ." Similar constructions recur throughout. After warning that dangling constructions are sometimes difficult to recognize, he repeatedly displays his own lack of recognition. For example: "It is good practice, when writing the first draft of the manuscript, to spell out all terms." Justification on the basis of ellipsis is specious. In addition, barbarisms such as "no question but that" are conspicuous and offensive in a book on writing. Other flaws in grammar, usage, and punctuation are too numerous to list.

In "A Personalized [sic] Summary," Day stated: "I have been associated with scientific books and journals for more than a quarter of a century." Such an association, alas, does not automatically confer literary skills or credentials for the instruction of others in writing. If it did, every scientist and every physician, after poring over volumes of scientific publications, would be able to write, and to teach writing, masterfully. A prevalent misconception is that employment on an editorial staff qualifies one to teach writing. But writing requires far more than copy-editing, and the soundest advice on writing comes from successful writers, not editors.

Day's "cookbook" has not achieved his stated purpose of helping scientists "prepare manuscripts that will have a high probability of being accepted for publication and of being completely understood when they are published." Rather, he has rehashed, in hit-or-miss fashion and in sophomoric style, oft-repeated "tips." A collection of notes does not a book make. Nor does the *publication* of a book (which escapes peer review) validate the contents. Unfortunately, however, in the minds of many the printed word is gospel.

It is not the verbal infelicities, grammatical infractions, or faulty punctuation—nor even the organizational flaws—that mar this book most seriously; it is the author's apparent superficial understanding of the rationale and the fundamental principles of good scientific exposition. The "think first, write later" concept, which relates clear writing to clear thinking and which identifies my own instruction, he completely ignores. Thus, ratiocination, an essential antecedent to competent scientific exposition, receives no attention. Further, the book is organized according to the order of the parts in a final typescript, not the order in which an author best proceeds through the systematic steps in the preparation of a manuscript for publication. In his discussion of bibliographic references, he writes little about *when* to cite, but focuses instead on how to cite. Physicians and scientists who seek to improve their writing deserve a more learned and authoritative guide than the spate of shallow, dilettantish how-to books and articles on scientific writing that have appeared in recent years under the authorship of nescient neophytes.

LOIS DEBAKEY, PHD
Professor of Scientific Communication
Baylor College of Medicine
Houston, TX 77030

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Radiation Safety for Laboratory Technicians. By Charles A Kelsey, PhD. 42 pp., illustrated. St Louis, MO, Warren H Green, 1983. $9.50 (softcover).

SOCIAL TOPICS

American Couples: Money, Work, Sex. By Philip Blumstein, PhD, and Pepper Schwartz, PhD. 656 pp. New York, William Morrow and Company, 1983. $19.95 (hardcover).

In addition to these listings, the Journal *will publish obituaries written by physician readers. Inquiries should first be made to the Editor.*

Ernesto de J. Barrios, MD, Elmhurst. Died December 23, 1981; age 63. He graduated from the Universidad de la Habana Facultad de Medicina y Farmacia in 1946. He was a Diplomate of the American Board of Dermatology and was a member of the New York County Medical Society and the Medical Society of the State of New York.

Daniel W. Berkowitz, MD, Rockville Centre. Died March 22, 1983; age 47. He graduated from the Universidad de Guadalajara Facultad de Ciencias Medicas y Biologicas in 1965 and was a member of the New York State Society of Anesthesiologists, the American Society of Anesthesiologists, the Nassau County Medical Society, and the Medical Society of the State of New York.

John Francis Connell, MD, Flushing. Died October 21, 1983; age 74. He graduated from Boston University School of Medicine in 1933 and was a Fellow of the American College of Allergists, and a member of the Medical Society of the County of Queens and the Medical Society of the State of New York.

Royal Stanton Davis, MD, New Rochelle. Died October 11, 1983; age 76. He was a graduate of Columbia University College of Physicians and Surgeons. Dr. Davis was a Fellow of the American Academy of Family Practice, the Medical Society of the County of Westchester, and the Medical Society of the State of New York.

Dimitry Simon Dibich, MD, Glen Cove. Died September 29, 1983; age 90. He was a graduate of Hahnemann Medical College and Hospital of Philadelphia. His memberships included the New York County Medical Society and the Medical Society of the State of New York.

Edward Francis Dodge, MD, Winona, Minnesota. Died September 25, 1983; age 79. Dr. Dodge was a graduate of the University of Buffalo School of Medicine. His memberships included the Academy of Medicine, the American Occupational Medical Association, the Medical Society of the County of Niagara, and the Medical Society of the State of New York.

Max Dosik, MD, Newburgh. Died August 24, 1983; age 74. Dr. Dosik attended Middlesex University School of Medicine, Waltham, and graduated in 1938. His memberships included the Medical Society of the County of Orange and the Medical Society of the State of New York.

Antonin A. Dostal, MD, Warwick. Died September 16, 1983; age 39. Dr. Dostal was a 1967 graduate of the Universita Karlova Fakulta Lekarska, Praha. He was a Diplomate of the American Board of Obstetrics and Gynecology and a member of the Medical Society of the County of Orange and the Medical Society of the State of New York.

Kumjian A. Durand, MD, Albany. Died November 30, 1976; age 79. Dr. Durand attended the University of Vermont College of Medicine and graduated in 1923. He was a member of the American Academy of Family Practice, the Medical Society of the County of Fulton, and the Medical Society of the State of New York.

Ann Emily F. Florsheim, MD, Cassadaga. Died September 27, 1983; age 86. Dr. Florsheim graduated from Thuringische, Landesuniversitat Medicine Fakultat, Jena, Thuringia in 1928. She was a Fellow of the American Academy of Family Practice and a member of the Medical Society of the County of Chautauqua and the Medical Society of the State of New York.

Albert Sidney Fox, MD, New York City. Died October 8, 1983; age 85. Dr. Fox attended the St. Louis University School of Medicine and graduated in 1931. He was a fellow of the American College of Surgeons and a Diplomate of the American Board of Ophthalmology. His memberships included the Academy of Medicine, the American Academy of Ophthalmology and Otolaryngology, the Pan American Association of Ophthalmology, New York County Medical Society and the Medical Society of the State of New York.

Samuel Galburt, MD, Brooklyn. Died June 14, 1983; age 82. Dr. Galburt graduated from New York Medical College, Flower and Fifth Avenue Hospitals in 1930. He was a qualified Fellow of the International College of Surgeons and a Diplomate of the American Board of Otolaryngology. His memberships included the American Academy of Otolaryngology, the American Academy of Facial Plastic and Reconstructive Surgery, the Medical Society of the County of Kings and the Medical Society of the State of New York.

Stanley S. Greenfield, MD, Brooklyn. Died July 15, 1983; age 74. He graduated from the University of Buffalo School of Medicine in 1934. Dr. Greenfield was a Diplomate of the American Board of Pediatrics and a member of the American Academy of Pediatrics, the American Public Health Association, the Medical Society of the County of Kings and the Medical Society of the State of New York.

Clara Hale Gregory, MD, Fayetteville. Died October 1, 1983; age 93. Dr. Hale graduated from the State University of New York Upstate Medical Center, Syracuse, in 1912 and was a member of the Onondaga County Medical Society and the Medical Society of the State of New York.

John Edward Hanawalt, MD, Hawthorne, Florida. Died September 25, 1983; age 92. He was a graduate of Hahnemann Medical College and Hospital of Philadelphia. His memberships included the Nassau County Medical Society and the Medical Society of the State of New York.

Ole A. Holtermann, MD, Buffalo. Died October 14, 1983; age 57. He graduated from the Kobenhavns Universitet Laegeviden-Skabelige Fakultet in 1954. Dr. Holtermann was a Diplomate of the American Board of Dermatology. His memberships included the American Academy of Dermatology, the Medical Society of the County of Erie and the Medical Society of the State of New York.

Juan Larralde, MD, New York City. Died October 8, 1983; age 78. Dr. Larralde graduated from the Universite de Paris Faculte de Medecine in 1932. He was a Diplomate of the American Board of Dermatology. His memberships included the Academy of Medicine, the New York State Dermatological Society, the American Academy of Dermatology, the New York County Medical Society and the Medical Society of the State of New York.

William Reese Lewis, MD, Lewiston. Died September 25, 1983; age 75. Dr. Lewis attended the University of Buffalo School of Medicine and graduated in 1932. He was a member of the Academy of Medicine, the Medical Society of the County of Niagara and the Medical Society of the State of New York.

Anthony Marazita, JD, MD, Bronx. Died September 19, 1983; age 79. He graduated from New York University College of Medicine in 1930. Dr. Marazita was a Qualified Fellow of the International College of Surgeons. His memberships included the New York State Surgical Society, the American Fertility Society, the Bronx County Medical Society and the Medical Society of the State of New York.

Justin William Mignault, MD, Baldwinsville. Died October 8, 1983; age 73. He was a graduate of the State University of New York Upstate Medical Center, Syracuse in 1933. His memberships included the American School Health Association, the Onondaga County Medical Society and the Medical Society of the State of New York.

Edgar A. Miller, MD, Jamestown. Died June 15, 1982; age 66. Dr. Miller attended the University of Maryland School of Medicine and graduated in 1942. He was a Fellow of the American College of Radiology and a Diplomate of the American Board of Radiology. He was a member of the Radiological Society of North America, Inc., the Medical Society of the County of Chautauqua and the Medical Society of the State of New York.

Francis X. Morrone, MD, Mt. Vernon. Died November 19, 1982; age 74. He graduated from Georgetown University School of Medicine in 1936 and was a Diplomate of the American Board of Otolaryngology. His memberships included the American Academy of Otolaryngology, the Medical Society of the County of Westchester and the Medical Society of the State of New York.

John Philip Murphy, MD, Kenmore. Died September 28, 1983; age 74. He was a 1935 graduate of Georgetown University School of Medicine. His memberships included the American Academy of Family Practice, the Medical Society of the County of Erie and the Medical Society of the State of New York.

Samuel Sidney Pasachoff, MD, Troy. Died October 7, 1983; age 79. Dr. Pasachoff was a graduate of New York University College of Medicine in 1929. He was a Fellow of the American College of Surgeons, and his memberships included the International Academy of Proctology, the Bronx County Medical Society and the Medical Society of the State of New York.

Lester Edwin Sanford, MD, Port Ewen. Died September 13, 1983; age 90. He graduated from Albany Medical College of Union University in 1916 and was a member of the Medical Society of the County of Ulster and the Medical Society of the State of New York.

Gerhart Steven Schwarz, MD, New York City. Died October 7, 1982; age 70. Dr. Schwarz graduated from the Universitat Basel Medizinische Fakultat in 1939. He was a Fellow of the American College of Radiology and a Diplomate of the American Board of Radiology. His memberships included the New York Roentgen Society, the Academy of Medicine, the American Roentgen Ray Society, the Radiological Society of North America, Inc., the Pan American Medical Association, the New York County Medical Society and the Medical Society of the State of New York.

Jesse A. Tolmach, MD, New York City. Died September 30, 1983; age 85. Dr. Tolmach attended Columbia University College of Physicians and Surgeons and graduated in 1921. He was a Diplomate of the American Board of Dermatology, Inc. His memberships included the Academy of Medicine, the New York State Dermatological Society, the American Academy of Dermatology, the Society for Investigative Dermatology, New York County Medical Society and the Medical Society of the State of New York.

Robert Joseph Tufano, MD, New Hyde Park. Died September 30, 1983; age 56. Dr. Tufano was a 1954 graduate of the State University of New York Downstate Medical Center. He was a Fellow of the American College of Obstetricians and Gynecologists, a Fellow of the American College of Surgeons, a Diplomate of the American Board of Obstetrics and Gynecology, a member of the American Fertility Society, the American Geriatrics Society, the Nassau County Medical Society and the Medical Society of the State of New York.

Francis Dario Vaccino, MD, Brooklyn. Died October 22, 1983; age 60. He was a graduate of the State University of New York Downstate Medical Center. Dr. Vaccino was a Diplomate of the American Board of Pediatrics and a member of the American Academy of Pediatrics, the Medical Society of the County of Queens and the Medical Society of the State of New York.

Edward T. Wilkes, MD, New York City. Died October 20, 1983; age 84. Dr. Wilkes graduated from Cornell University Medical College in 1921. He was a Diplomate of the American Board of Pediatrics and was a member of the New York Pediatric Society, the American Academy of Pediatrics, the Medical Society of the County of Queens and the Medical Society of the State of New York.

Raymond M. Williams, MD, White Plains. Died October 14, 1983; age 63. He graduated from Jefferson Medical College of Philadelphia in 1944. Dr. Williams was a Fellow of the American College of Surgeons and a Diplomate of the American Board of Surgery. His memberships included the Academy of Medicine, the Medical Society of the County of Westchester and the Medical Society of the State of New York.

Guidelines for authors

ORIGINALITY

The *New York State Journal of Medicine* welcomes research papers and original essays on the practice of medicine, medical education, public health, the history of medicine, medicolegal matters, legislation, ethics, the mass media and socioeconomic issues in health care.

Manuscripts should be prepared according to the "Uniform requirements for manuscripts submitted to biomedical journals" (*NY State J Med* 1983; 83:1089–1094). The requirements were established by the International Committee of Medical Journal Editors, of which the *Journal* is a participating member. These Guidelines are intended to highlight aspects of the *Journal*'s particular style of publication.

A manuscript will be considered for publication if it is original, has not been published previously in whole or in part in either a medical journal or a lay publication, and is not simultaneously under consideration elsewhere. A copy of any possibly duplicative material, such as a reference "in press," should be submitted along with the manuscript.

PREPARATION

An original typewritten or "word-processed" manuscript and two photocopies (to facilitate outside review) are required. If the manuscript is not accepted for publication, the original and one copy will be returned. All figures must be submitted in triplicate. The manuscript should be double-spaced throughout, including references, tables, legends, quotations, and acknowledgments. A separate title page should include the full title of the paper in upper and lower case type, the names of the authors exactly as they should appear in print (including their highest academic degree), an abbreviated title of no greater than 40 spaces for use as a running foot, and the names of all providers of funding for research on which the paper is based. Information on the amount and allocation of funding is optional.

A corresponding author should be designated in the covering letter. Authors should list their title and affiliation at the time they did the work, and, if different, their present affiliation. The addresses and telephone numbers of all authors should be supplied for editorial purposes. All authors of a manuscript are responsible for having read and approved it for submission.

CATEGORIES

Research Papers should be limited to 2,500 words and should include the following sections: Introduction, Methods, Results, Discussion, and References. Multiple subheadings and numbered lists are discouraged. An abstract limited to 150 words should state the reasons for the study, the main findings, and their implications. Statistical evaluations should be described in the Methods section, and the name and affiliation of the statistician should be included in the acknowledgments if this individual is not listed as a coauthor. Reports of experiments involving human subjects must include a description in the Methods section of the informed consent obtained and a statement that the procedures followed were approved by an institutional research review committee. Anonymity of patients must be preserved. Reports of experiments on animals must note which guidelines were followed for the care and use of laboratory animals.

Case Reports should be limited to 1,250 words. Review Articles should not exceed 3,000 words. Commentaries should be between 750 and 1,000 words. Other kinds of original essays should not exceed 2,000 words. A letter of inquiry should be sent to the editor prior to submitting a Review Article or Commentary.

For Research Papers only, scientific measurements should be given in conventional units, with Système Internationale (SI) units in parentheses. Abbreviations and acronyms should be kept to a minimum, and jargon should be avoided. Generic names of drugs should be used instead of brand names.

FIGURES

The submission of color illustrations or slides is discouraged. Only black and white glossy photographic prints or "camera-ready" artwork will be accepted. The *Journal* is unable to provide art services such as the addition of arrows to photographs. A signed consent for publication must accompany photographs in which the patient is identifiable. Illustrations from other publications generally will not be considered. Legends for illustrations should be typed on a separate sheet, and for photomicrographs should include magnification and stain. Each illustration should be lightly marked on the back in pencil with the name of the first author, the number as cited in the text, and an arrow indicating the top. Each set of illustrations should be submitted unmounted in a separate envelope.

Tables should be simple, self-explanatory, and few in number. Each table should be typed double-spaced on a separate sheet.

REFERENCES

References should be limited to the most pertinent. The recommended maximum number of references is 25 for Research Papers and most other original contributions (except lengthier Review Articles), 12 for Commentaries and Case Reports, and six for letters to the editor.

Authors are responsible for the accurate citation of references. Citation of secondary sources is discouraged except where the original reference is unobtainable. Authors may not cite references they have not read, and the use of abstracts as references should be avoided.

References should be indicated in the text by superscript numbers following the name of the author (eg, Smith[2] reported two cases).

The list of references at the end of the article should be typed double-spaced and references should be numbered in the order in which they appear on the text. When there are six or fewer authors, all should be listed; where there are seven or more, the first three should be listed, followed by *et al.* Names of journals should be abbreviated according to *Index Medicus* and underlined.

Sample references:

1. Kepes ER, Thomas P, Vemulapalli K: Methadone and intravenous morphine requirements. *NY State J Med* 1983; 83:925–927.
2. McGuigan JE. Peptic ulcer. In: Petersdorf RG, Adams RD, Braunwald E, Isselbacher KJ, Martin JB, Wilson JD, eds. *Harrison's Principles of Internal Medicine*. New York, McGraw-Hill, 1983, pp 1697–1712.

REVIEW

All manuscripts are reviewed by the editors, and most manuscripts are sent to outside referees. Decisions concerning acceptance, revision, or rejection of a manuscript are usually made within three to six weeks. Every effort will be made to assure prompt publication of an accepted manuscript. A galley proof will be sent to the author for approval prior to publication.

Address correspondence to Alan Blum, MD, Editor, *New York State Journal of Medicine*, P.O. Box 5404, 420 Lakeville Road, Lake Success, NY 11042.

1984 Albion O. Bernstein, M.D. Award

The Medical Society of the State of New York is accepting nominations for the 1984 ALBION O. BERNSTEIN, M.D. AWARD until June 1, 1984.

This national award is given to a physician, surgeon, or scientist who has recently made a widely beneficial scientific discovery in medicine, surgery or the prevention of disease. Recent winners include, Baruch S. Blumberg, M.D., Ph.D., Manfred M. Mayer, Ph.D., Georges Köhler, Ph.D., Wylie W. Vale, Ph.D. and Hugh O'Neill McDevitt, M.D.

The $2,000 award and appropriate scroll will be presented at the annual meeting of the Medical Society of the State of New York, October 14–17, 1984. The award was endowed by the late Morris J. Bernstein in memory of his son, a physician who died in an accident while answering a hospital call in November 1940.

Nominators must complete and submit an official nomination form with additional support information which must include the nominee's curriculum vitae, a brief synopsis of the significance of the achievement and a list of publications, if any. Please submit by June 1, 1984.

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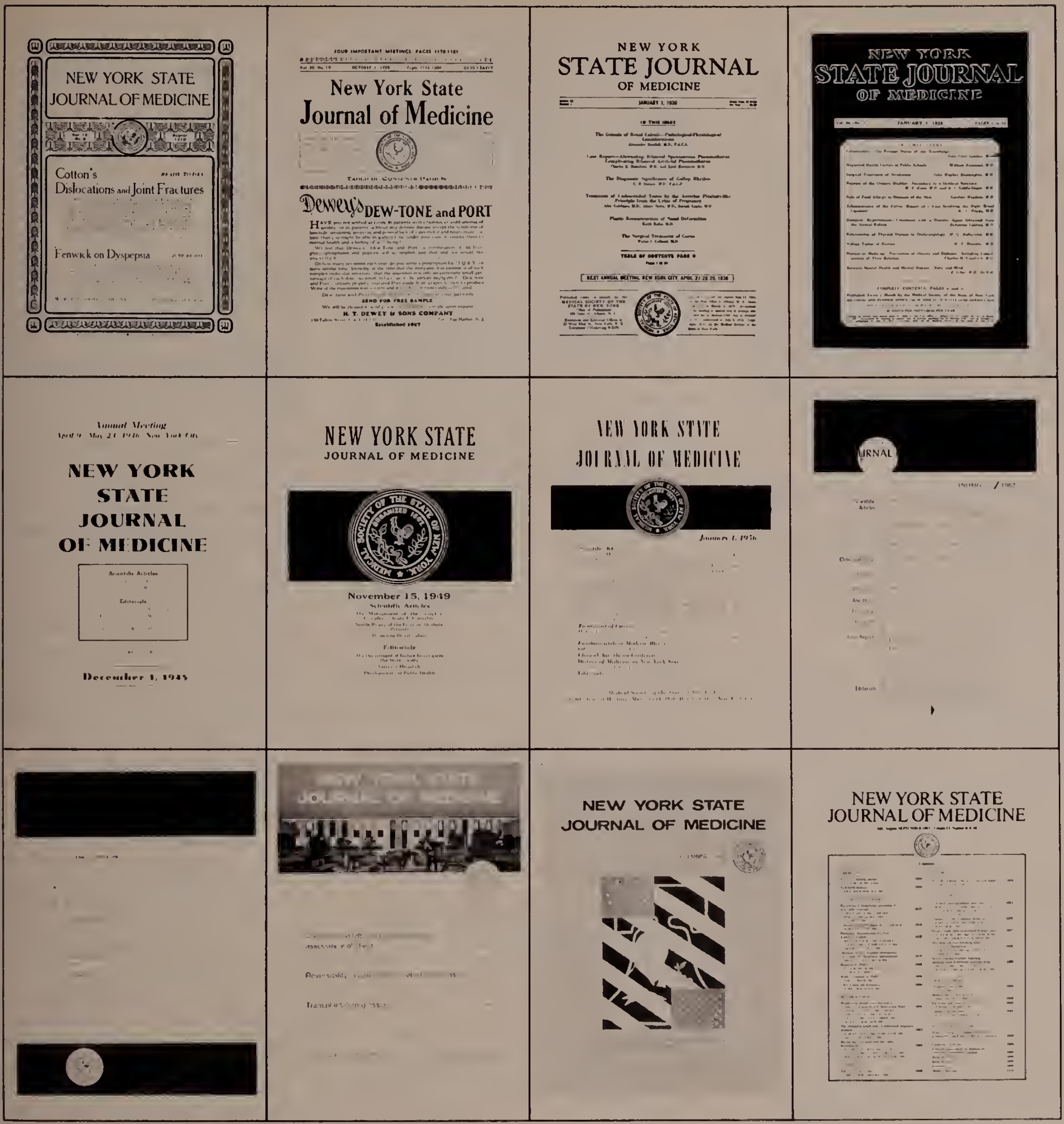

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MEETINGS AND LECTURES

APRIL 1984

AROUND THE STATE

MANHATTAN

Apr. 2. **Metabolic and Endocrine Effects of Alcohol; Modern Neurological and Psychiatric Aspects of Alcoholism in Man.** 2 Cat 1 credit. Info: Otto C Kestler, MD, 515 Madison Ave, New York, NY, 10022. Tel: (212) 758-2590.

Apr 3–Nov 16. **Emergency Medicine Board Review.** 63 Cat 1 credit. *Apr 26–28.* **Update in Dermatology.** 16 Cat 1 credits. Info: Ms Elaine Breslow, NYU Post-Graduate Medical School, 550 First Avenue, New York, NY 10016. (212) 340-5295 (24 hr service).

Apr 4. **Electrotherapy; Therapeutic Electromyograph.** Info: Wanda Brodzka, MD, Program Committee, New York Society of Physical Medicine and Rehabilitation, 136 St and Lenox Ave, New York, NY 10037. Tel: (212) 491-8357.

Apr 5. **Lung Cancer: Diagnosis and Treatment.** 1½ Cat 1 credit. Info: Clifford L Spingarn, MD, Chairman, Committee on CME, Doctors Hospital, 170 East End Ave, New York, NY 10028. Tel: (212) 870-9000.

Apr 5–7. **New Diagnostic and Therapeutic Modalities in Cardiovascular Disease.** 15 Cat 1 credit. Info: Ronald J Sanchez, American College of Cardiology, 9111 Old Georgetown Rd, Bethesda, MD 20814. Tel: (301) 897-5400.

Apr 6. **Contact Ocular Ultrasonography in Clinical Practice.** 6 Cat 1 credit. *Apr 14.* **Recent Advances in Anorectal Surgery.** 6 Cat 1 credit. *Apr 27.* **The Use of CO_2 Lasers in Surgery.** 6 Cat 1 credit. *Apr 27.* **Symposium of Cardiac Rehabilitation.** 6.5 Cat 1 credit. *Apr 27.* **The Medical Benefits of Risk Reduction Through Nutritional and Lifestyle Changes.** Info: The Page and William Black Postgraduate School of Medicine of The Mount Sinai School of Medicine, One Gustave Levy Pl, New York, NY 10029. Tel: (212) 650-6546(6737).

Apr 6. **New Drug Therapy.** Info: Bernadine T Ensor, Communications Media for Education, PO Box 712, Princeton JCT, NJ 08550. Tel: (609) 799-2300.

Apr 6–8. **Advanced Cardiovascular Diagnostic and Therapeutic Methods.** 18 Cat 1 credit. Info: Ms Mary A Schroeder, Educ Coord, International Medical Education Corporation, 64 Inverness Drive East, Englewood, NJ 80112. Tel: (800) 525-8651; (303) 790-8445, ext 123.

Apr 9. **Depression and Somatic Illness.** *Apr 16.* **Medical Aspects in Quality Assurance Review.** *Apr 30.* **Psychopharmacology: Fundamentals and New Developments in Relation to Ability to Work.** Info: Harry R Pace, MD, New York State Dept of Social Services, Office of Disability Determination, 110 William St, New York, NY 10038. Tel: (800) 522-5511; (212) 587-3770.

Apr 11. **The Physician's Guide to Type II Diabetes: Diagnosis and Treatment.** (via satellite). Info: American Diabetes Association, PO Box 768, New York, NY 10159. Tel: (800) 221-2207; (212) 460-5900.

Apr 11 and 25. **Emergency Procedures Workshop.** Info: Wayne Longmore, MD, Emergency Care Institute, Bellevue Hospital Center, First Ave and 27th St, New York, NY, 10016. Tel: (212) 561-6561.

Apr 14. **Hand Rehabilitation Seminar.** Info: Yasoma Challenor, Dept of Rehab Med, Harlem Hospital Center, Lenox Ave at 135th St, New York, NY 10037. Tel: (212) 491-1467.

Apr 20. **Clinical Pathologic Correlations of Hematuria in Children.** Info: Victor Tchertkoff, MD, Coordinator, Metropolitan Hospital Center, 1901 First Ave, New York, NY 10029. Tel: (212) 360-6253.

Apr 24. **Psychological Reactions of Spouses to Critical Illness.** Cat 1 credit. Info: Mrs V Matthes, Admin Secy, Society for Liaison Psychiatry, 542 Baldwin Ave, Baldwin, NY 11510. Tel: (516) 379-1787.

Apr 24–27. **The Interspecialty Facial Surgery Congress for Aesthetic, Cancer and Reconstructive Surgery.** Info: Ms J Weschner, c/o Pierre Guibor, MD, The International Oculoplastic Society, Inc., 630 Park Ave, New York, NY 10021. Tel: (212) 734-1010 or (800) 223-4500.

Apr 25. **Update Your Medicine.** Info: Lila A Wallis, MD, Association of Practicing Physicians of the New York Hospital, 1300 York Ave, Room D-115, New York, NY 10021. Tel: (212) 737-4444, or Dena Toussaint (212) 472-6119.

Apr 30–May 4. **Electromyography and Electrodiagnosis.** 31 Cat 1 credit. Info: Daoud B Karam, MD, New York Medical College, Rehabilitation Medicine, Coler Memorial Hospital, Roosevelt Island, NY 10044. Tel: (212) 688-9400, ext 385.

BRONX

Apr 26. **Urban Hospitals—Partners in Neighborhood Preservation.** Info: Public Interest Dept, Montefiore Medical Center, 111 E 210 St, Bronx, NY 10467. Tel: (212) 920-4011.

Apr 27–28. **Advanced Trauma Life Support Course.** Info: William M Stahl, MD, Chairman, New York-Brooklyn Committee on Trauma, Lincoln Medical and Mental Health Center, 234 E 149 St, Bronx, NY 10451. Tel: (212) 579-5900.

BROOKLYN

Apr 8. **Diagnosis and Management of Stroke.** Info: Miss Hazel Spadafora, Executive Dir, Kings County Medical Society, 1313 Bedford Ave, Brooklyn, NY 11216. Tel: (212) 467-9000.

Apr 9. **Special Problems of the Premature Infant.** *Apr 10.* **Anesthesia and Postoperative Care for Pediatric Cardiovascular Surgery.** 1 Cat 1 credit per lecture. Info: Abraham I Raskob, MD, Chairman, CME Committee, Dept of Anesthesiology, SUNY Downstate Medical Center, 450 Clarkson Ave, Brooklyn, NY 11203. Tel: (212) 270-1233.

QUEENS

Apr 3. **Rational Choice of Antibiotics and Antimicrobial Prophylaxis.** *Apr 10.* **Jaundiced Patient: A Clinical Algorithm.** 1½ Cat 1 credit. Info: Luisa T. Gonzalez, Coordinator, CME, Flushing Hospital and Medical Center, 4500 Parsons Boulevard, Flushing, NY 11355. Tel: (212) 670-5741.

Apr 3. **The Changing Spectrum of In-**

fectious Diseases. *Apr 10.* **Non-Infectious Granulomatous Lung Diseases.** *Apr 24.* **Slow Virus Diseases.** Info: Clo Vezza, Booth Memorial Medical Center, Health Education Center, 65-45 Main St, Flushing, NY 11355.

NASSAU

Apr 4. **Neuro-Ophthalmology.** 7 Cat 1 credit. Info: Ann J Boehme, Continuing Education Coordinator, Long Island Jewish-Hillside Medical Center, New Hyde Park, New York 11042. Tel: (212) 470-2114.

Apr 4. **The Role of Forensic Science in Public Health.** Info: Edwin Poulter, New York State Public Health Association, Long Island Region, 240 Old Country Road, Mineola, NY 11501. Tel: (516) 535-2016.

Apr 6. **Parenteral Nutrition in the High Risk Neonate.** *Apr 13.* **Fetal and Neonatal Carbohydrate Metabolism and its Disorders.** *Apr 27.* **Cardiovascular Problems in the Neonate.** Info: Nergesh Tejani, MD, Ob-Gyn, Nassau County Medical Center, 2201 Hempstead Turnpike, East Meadow, NY 11554. Tel: (516) 542-2257.

Apr 6. **Psychological Aspect of Genetic Screening.** *Apr 13.* **Pharmacology and Clinical Use of the Benzodiazepines.** *Apr 20.* **Neuropsychology and Psychiatry.** Info: Clement Boccalini, MD, Nassau County Medical Center, 2201 Hempstead Turnpike, East Meadow, NY 11554. Tel: (516) 542-0123.

Apr 11. **Oncology-Hematology Symposium on Curability of Leukemia, Lymphoma, Germ Cell Neoplasia, and Breast Cancer.** Info: Office of Medical Education, Nassau Hospital, Mineola, NY 11501. Tel: (516) 663-2521.

Apr 26-27. **Update on Evoked Potentials, Macro and Single Fiber EMG.** 12 Cat 1 credit. Info: Arminius Cassvan, MD, Nassau County Medical Center, 2201 Hempstead Turnpike, East Meadow, NY 11554. Tel: (516) 542-0123.

SUFFOLK

Apr 5. **Cancer and A.I.D.S.** 4 Cat 1 credit. Info: Mr Ernest A Howell, Education Dir, American Cancer Society, Long Island Division, Inc., 535 Broad Hollow Rd, Melville, NY 11747. Tel: (516) 420-1111.

Apr 3. **Feeding the Neonate in the Hospital.** *Apr 10.* **Pediatric and Adolescent Medicine: Hepatitis.** Info: Arthur Schwager, MD, Chairman, Pediatric CME, Huntington Hospital, 270 Park Ave, Huntington, NY 11743. Tel: (516) 427-0530.

Apr 11. **The Use of Psychotropic Drugs in the Elderly.** Peekskill. Info: Sally Jo Tourjee, Harlem Valley Psychiatric Center, Wingdale, NY 12594. Tel: (914) 832-6611.

ERIE

Apr 12. **Tumors Involving the Skin.** Info: Gayle Bersani, RN, Cancer Control Coordinator, Roswell Park Memorial Institute, 666 Elm St, Buffalo, NY 14263. Tel: (716) 845-4406.

Apr 26-27. **An Institute on Hospice Care.** Info: Hospice Buffalo, Inc, Insti-

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4/26-4/28	Update in Dermatology
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5/3-5/5	The Medicolegal Autopsy
5/10-5/13	CT of the Spine (Grand Hyatt Hotel)
5/19-5/20	Review of Basic Sciences in Urology
5/19-5/20	Proficiency in Cytopathology
5/19-5/20	Practical Management of Gynecologic Endocrine Disorders and Infertility
JUNE	
6/4-6/6	Obstetrical Ultrasound
6/4	Interventional Radiology and Digital Imaging
6/5-6/9	Computed Tomography Head to Toe with MRI
6/11-6/15	Emergency Medicine
6/23 & 6/24	Chymopapain I & II (2 intensive 1 day sessions)
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AUGUST	
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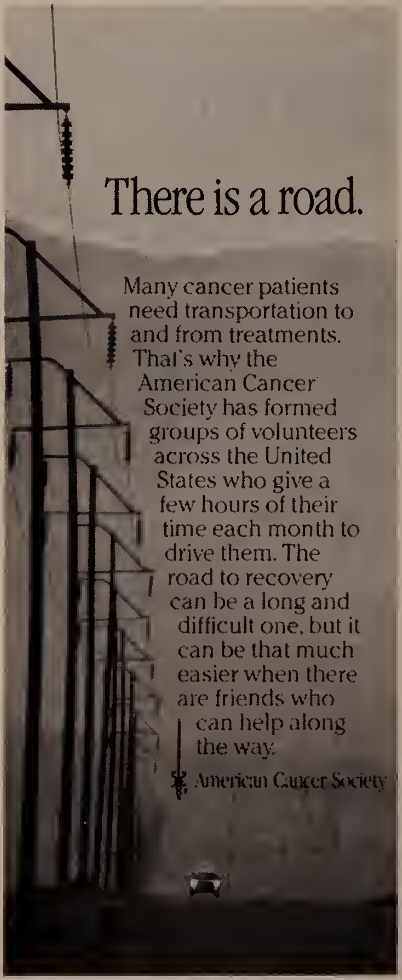

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American Cancer Society

This space contributed as a public service.

tute '84, 2929 Main St, Buffalo, NY 14214. Tel: (714) 838-4438.

ROCKLAND

Apr 3. **Intestinal Pseudo-Obstruction.** *Apr 10.* **Drug Induced Hepatitis.** *Apr 24.* **'Funny' Viral Hepatitis.** Info: Clinical Dept Directors' Office, Nyack Hospital, North Midland Ave, Nyack, NY 10960. Tel: (914) 358-6200, ext 2509.

ST LAWRENCE

Apr 19. **Thyroid Function and Interpretation of New Laboratory Testing.** Info: Sebastian A Mazzotta, MD, Program Chairman, Medical Society of the County of St Lawrence, Canton-Potsdam Hospital, 50 Leroy St, Potsdam, NY 13676. Tel: (315) 265-3300, ext 4202.

AROUND THE NATION

ARIZONA

Apr 8-11. **American College of Emergency Physicians Symposium.** 20 Cat 1 credit. Scottsdale. Info: Judy Albert, ACEP, PO Box 619911, Dallas, TX 75261. Tel: (214) 659-0911.

Apr 12-14. **Trauma Arts Festival.** 16 Cat 1 credit. Lake Powell. Info: Randy W Hale, EMS Training Coordinator, Northern Arizona Council of Governments, PO Box 57, Flagstaff, AZ 86002. Tel: (602) 774-1895.

Apr 14-21. **Updates in Pulmonary Medicine,** 24 Cat 1 credit. Lake Powell. *Apr 21-28.* **Neurological Emergencies.** 24 Cat 1 credit. Lake Powell. Info: Teena Hieb, EPIC Expeditions, PO Box 209G, Sun Valley, ID 83353. Tel: (208) 788-4995.

CALIFORNIA

Apr 6-8. **Sexual Issues in Medical Practice.** 14 Cat 1 credit. San Francisco. Info: Sara Borel, Extended Programs in Medical Education, U Cal School of Medicine, Room U-569 San Francisco, CA 94143. Tel: (415) 666-4251.

Apr 12-14. **Financing Human Services: State Options.** San Francisco. Info: Dick Stern, National Conference of State Legislatures, 1125 17th St, Suite 1500, Denver, CO 80206. Tel: (303) 292-6600.

NOSE HYGIENE

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MEDICAL SOCIETY OF THE
STATE OF NEW YORK
1984 CME ASSEMBLY
JUNE 29-JULY 1
Sheraton Centre, New York City

Doctor . .

Do you, or a physician you know, have a problem with alcoholism, drug abuse, emotional illness or other difficulties which interfere with the ability to practice medicine?

If so, please contact the Medical Society of the State of New York's Physicians' Committee, whose function is to assist impaired physicians, at the following confidential number: 516-488-7777.

Fundamental personnel management techniques

Recruiting and selection techniques
Getting the best possible employees

Training
Methods that work

Job evaluation
Performance review and how to do it
Terminating an employee—how to

Salary review
When and how should it be done

Developing job descriptions
To reduce confusion and job conflicts
To improve communications

Improving personnel utilization through task analysis
Making it possible to enlarge jobs and shift tasks among employees

Personnel problems question and answer session

Half-day workshop registration fees:
$65—members/staff
$75—nonmembers/staff

Better collections, billing and insurance methods

Collections
Cutting collection costs
Improving your collections percentages
Patient education
Collecting more effectively at the front desk
Establishing a definitive collection policy
Collection techniques that improve your cash flow
How to use the phone to collect
Aged trial balance and its use
Collection agencies and other ways to deal with delinquent accounts

Billing
Reducing the number of statements you send
Designing charge tickets that serve as take-home statements
Point-of-service collection beats billing
The Super Bill reduces paperwork
Micro-billing saves time and money
Accounts receivable system review and checklist

Billing
How to cut down on insurance processing costs
Physician education
Patient education
Use of standard insurance forms
The Super Bill: reduce insurance billing by 50%
Communicating with insurance companies
The Insurance claims log: makes follow-up easy

Accounts payable review
Check writing systems
Invoice handling
Petty cash
Refunds
Profitable use of your bank deposits

Half-day workshop registration fees:
$65—members/staff
$75—nonmembers/staff

Reception and patient flow techniques

Appointment scheduling control
Improving patient service
Dealing with key problems: work-ins, no-shows, cancels
Designing your own scheduling system
Modified wave techniques—they actually work!
Hourly control, daily control
Effective patient-recall systems

Improved telephone management
Telephone policies and how to develop them
Telephone procedures checklist—working tools for anyone answering the telephone
How to curb telephone interruptions of physicians and back office personnel
New equipment ideas
Telephone tips

Front office strategy
Cutting down on logjams at front desk

Medical records
Filing systems that work for you: alphabetical vs numerical
Cutting down on "lost" charts
Dictation and typing tips
Active-inactive-retired records and how to handle them

Half-day workshop registration fees:
$65—members/staff
$75—nonmembers/staff

Use of computers in medical practice (not a technical course in data processing)

Computer billing systems—Options
Service bureaus—batch billing
Service bureaus—on-line systems
Owning your own computer

Service bureaus—Batch billing
How it works for your office
Costs of these services
What sort of volume justifies using this service?
How to check out this service
Things to watch out for

Service bureaus—On-line systems
How they work in your office
Costs of these services
Advantages over batch billing systems
When should you consider this type of system?
What questions should you ask to check this out?
Traps to avoid

Owning your own computers
Comparing mini-computers and micro-computers
State of the art
Cost comparisons
Software—programming considerations
Pitfalls—learn from other physicians' mistakes

General considerations
Conversion problems: costs, personnel considerations; timetables
How will your patients accept something different?
What reports do you need? Do you need computerization to get these reports?

Full-day workshop registration fees:
$125—members/staff
$150—nonmembers/staff

Practice development techniques

Practice building with current patie s
How to hold on to them
Scheduling considerations

Patient satisfaction surveys
How to design one
How to get best results
Other ways to monitor your patients' attitudes towards your practice

Should you use a newsletter?
What should it contain?
Circulation
Other ways of communicating

Attracting new patients
How to analyze and develop your best referral sources
Innovative office hour considerations
Facilities/location considerations

Developing a logbook
How to manage it and what to do with

Patient information brochures
How to develop one for your practice
Distribution for maximum effectivenes

Community exposure
Marketing ideas that have worked for c er practices

Involving your office staff
What can they do?

Improved physician/patient communications
Tips on patient pleasers

Half-day workshop registration fees
$65—members/staff
$75—nonmembers/staff

Workshop materials

Each workshop features a workbook p ed with practical information usable at the workshops and for your medical office reference shelf.

CEU's (continuing education uni)

The American Association of Medical Assistants will award .3 CEU's for attendance at each ½ day workshop ar .6 CEU's for each full day workshop.

Tax deduction for education expenses

Treasury Department regulation 1.162- permits an income tax deduction for educational expenses (registration fee and cost of travel, meals and lodging) undertaken to maintain or improve skill required in one's employment or other t le or business.

Registration Information

- A complete schedule, with workshop locations, is on the following page
- Registration is open to physicians and their staffs
- Registration is limited and available on a first-come, first-serve basis
- Registration is not completed until both the registration form and fee are submitted.
- Reduced registration fees apply to member physicians and their staffs
- Physicians can qualify for the reduced fees for themselves and their staffs by submitting a completed application and dues no later than one week before the workshop
- Refunds will be given only if requested at least one week prior to the workshop
- Registration fees (per participant):

Half-day workshops:	$65 for members & their staffs $75 for nonmembers and their staffs
Use of computers in medical practice:	$125 for members & their staffs $150 for nonmembers & their staffs

- For additional information, call MSSNY's Division of Membership, (516) 488-6100, extension 252

Registration form

Please make your check payable to MSSNY and mail with registration form to:
MSSNY Workshops, 420 Lakeville Rd., Lake Success, NY 11042.

Please register me to attend:

☐ Personnel management techniques:	☐ Lake Success (April 10)	☐ Rochester (May 8)
☐ Better collections, billing & insurance:	☐ Lake Success (April 11)	☐ Rochester (May 9)
☐ Reception & patient flow techniques:	☐ Lake Success (April 11)	☐ Rochester (May 9)
☐ Use of computers in medical practice:	☐ Westchester (April 12)	☐ Rochester (May 10)
☐ Practice development techniques:	☐ Westchester (April 13)	☐ Rochester (May 11)

Enclosed is my ☐ member ☐ nonmember registration fee of $ ________ each for myself, and/or my staff

Registrant's name ______________________________

Physician employer's name (if applicable) ______________________________

Office address ______________________________

______________________________ Telephone ______________

☐ Please send me membership information so I, too, can qualify for the reduced registration fee.

☐ I can't attend now. Please advise me of future workshops.

To register more than one person, please copy this form or type complete information on separate sheet.

The Medical Society of the State of New York

presents

Medical Practice Workshops For Physicians and Their Staffs

Fundamental Personnel Management Techniques

Tuesday,	Tuesday,
April 10, 1984	May 8, 1984
Lake Success, NY	Rochester, NY

Better Collections, Billing and Insurance

Wednesday,	Wednesday,
April 11, 1984	May 9, 1984
Lake Success, NY	Rochester, NY

Reception and Patient Flow Techniques

Wednesday,	Wednesday,
April 11, 1984	May 9, 1984
Lake Success, NY	Rochester, NY

Use of Computers in Medical Practice

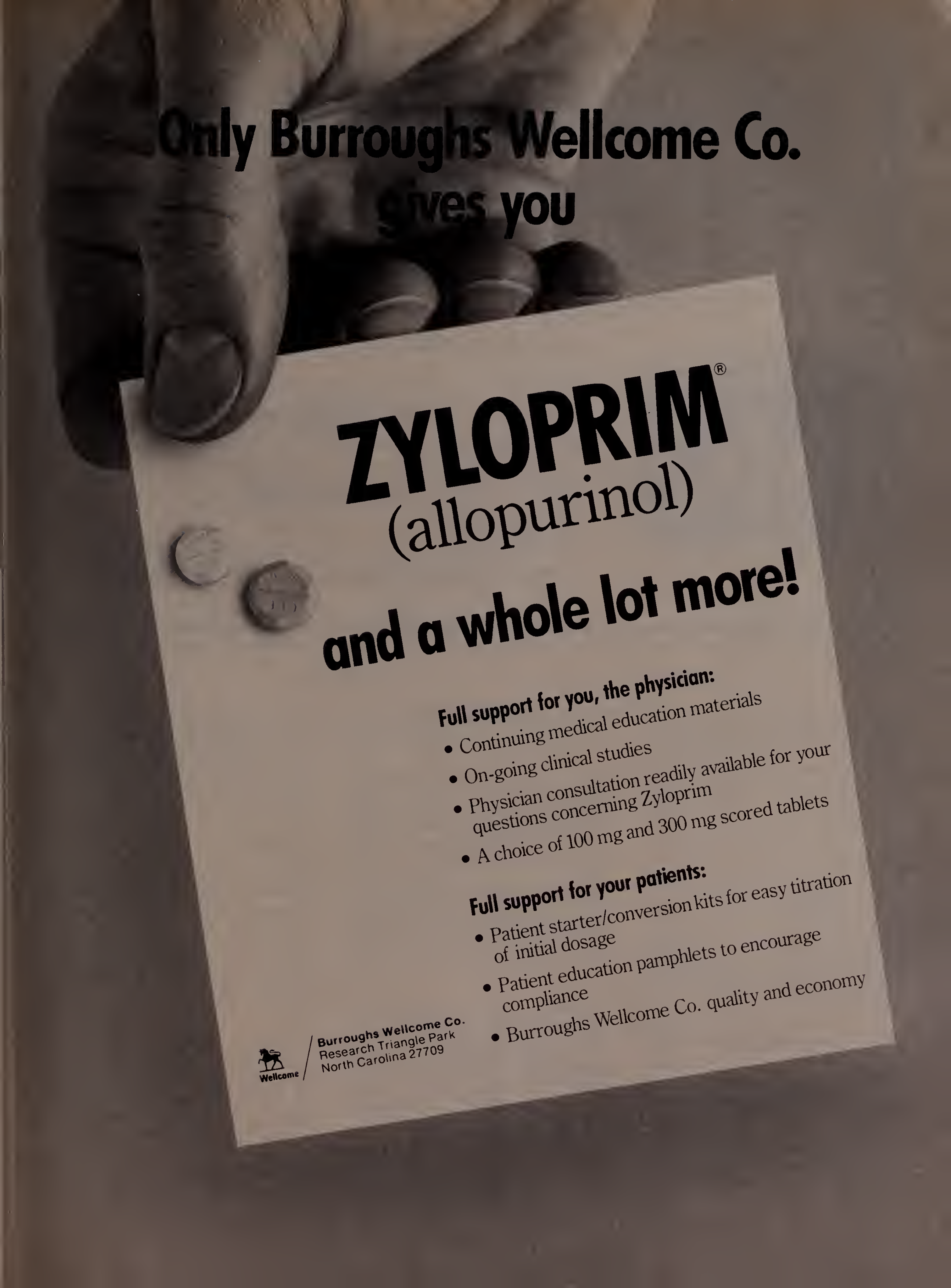
Thursday,	Thursday,
April 12, 1984	May 10, 1984
Westchester*	Rochester, NY

Practice Development Techniques

Friday,	Friday,
April 13, 1984	May 11, 1984
Westchester*	Rochester, NY

All workshops are conducted by Conomikes Associates, Inc.—nationally known productivity consultants for the health professions. Conomikes workshops have been sponsored by 25 state medical societies and the American College of Obstetricians and Gynecologists; American Academy of Orthopaedic Surgeons; American Council of Otolaryngology; American Association of Ophthalmology; American Academy of Dermatology; American Society of Internal Medicine, and American Academy of Family Physicians.

*Westchester location to be announced.



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Apr 12–14. **Current Emergency Diagnosis and Treatment.** 18 Cat 1 credit. San Francisco. Info: Terrie Van Alen, Extended Programs in Medical Education, U of Cal School of Medicine, Room U-569, San Francisco, CA 94143. Tel: (415) 666–4251.

FLORIDA

Apr 4–7. **Physiology of Fitness.** 20.5 Cat 1 credit. Orlando. *Apr 12–14.* **Critical Care Medicine.** 16 Cat 1 credit. Lake Buena Vista. Info: Mrs Cindy Shenk, Orlando Regional Medical Center, 1414 S Kuhl Ave, Orlando, FL 32806. Tel: (305) 841–5144.

Apr 6–8. **How Payment Changes Affect Your Practice.** West Palm Beach. Info: Jeanette Stone, Southern Medical Association, PO Box 2446, Birmingham, AL 35210. Tel: (205) 323–4400.

Apr 6–8. **Family Practice Update.** 18 Cat 1 credit. Clearwater Beach. Info: Mabel A Costine, Asst. DME, Sun Coast Hospital, PO Box 2025, Largo, FL 34294–2025. Tel: (813) 581–9474.

Apr 8–13. **Colorectal Cancer Screening Strategy on the Use of Flexible Sigmoidoscopy.** 15 Cat 1 credit. Orlando. Info: Hurley Medical Center, Institute for CME, 1 Hurley Plaza, Flint, MI 48502. Tel: (313) 257–9142.

Apr 16–20. **Family Practice Review.** 24 Cat 1 credit. Kissimmee. Info: Grace Wagner, U of Florida, Box J233, JHM Health Center, Gainesville, FL 32610. Tel: (904) 392–3143.

GEORGIA

Apr 26–29. **American College of Physicians Annual Session.** Atlanta. Info: Annual Session Division, American College of Physicians, 4200 Pine St, Philadelphia, PA 19104. Tel: (215) 243–1200.

HAWAII

Apr 14–21. **Problems and Controversies in Emergency Medicine.** 21 Cat 1 credit. Maui. Info: Edith S Bookstein, U of Cal-San Diego School of Medicine and American Institute of Postgraduate Education, PO Box 2586, La Jolla, CA 92038. Tel: (619) 454–3212.

INDIANA

Apr 23–27. **Electrocardiographic Interpretation of Complex Arrhythmias: A Physiologic Approach.** 33.5 Cat 1 credit. Indianapolis. Info: Extramural Programs Dept, American College of Cardiology, 9111 Old Georgetown Road, Bethesda, MD 20814. Tel: (301) 897–5400, ext 226.

IOWA

Apr 18. **Update on GI Disease.** 6 Cat 1 credit. Des Moines. Info: D J Lulu, MD, Dir Med Ed, Mercy Hospital Medical Center, 6th and University, Des Moines, IA 50314. Tel: (515) 247–3042.

Apr 23–24. **Genetics and Teratology Update.** 13 Cat 1 credit. Iowa City. Info:

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East Meadow, L. I.
New York 11554
(516) 683-2565/2566

Eastern New York State
Navy Medical Programs
Navy Recruiting District
O'Brien Federal Building
Albany, New York 12207
(518) 472-4427/4463

Western New York State
Navy Medical Programs
Federal Building
111 West Huron Street
Buffalo, New York 14202
1-800-822-8838

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Upjohn Co. 29A
U.S. Navy 17A

Dept of Ob/Gyn, The University of Iowa College of Medicine, Iowa City, IA 52242. Tel: (319) 353-2121.

KANSAS

Apr 9–10. **Pediatric Emergencies.** 16 Cat 1 credit. *Apr 25–26.* **Postgraduate Family Practice Symposium.** 14 Cat 1 credit. *Apr 27.* **Annual Infectious Diseases Symposium.** 16 Cat 1 credit. Info: Jan Johnston, U of Kansas Medical Center, Office of Cont Ed, Rainbow at Olathe Blvd, Kansas City, KS 66103. Tel: (913) 588-4480.

LOUISIANA

Apr 12–13. **Emergi-Centers: An Alternative Health Care System.** 10 Cat 1 credit. New Orleans. Info: Thomas R O'Donovan, MD, American Academy of Medical Administrators, 30555 Southfield Road, Suite 525, Southfield, MI 48076. Tel: (313) 540-4310.

MARYLAND

Apr 1–3. **Medicare and Medicaid Payment Issues.** Baltimore. Info: Registrar, American Hospital Association, PO Box 98946, Chicago, IL 60693. Tel: (312) 280-6083.

MASSACHUSETTS

Apr 2–4. **Genetics and the Law.** 18 Cat 1 credit. Boston. Info: American Society of Law & Medicine, 765 Commonwealth Ave, Boston, MA 02215. Tel: (617) 262-4990.

Apr 2–4. **The Management of Medical and Surgical Emergencies.** 22 Cat 1 credit. *Apr 23–27.* **Clinical Endocrinology.** 35 Cat 1 credit. Boston. Info: Harvard Medical School, Dept. Cont Ed, Boston, MA 02115 Tel: (617) 732-1525.

Apr 7–8. **Coping with Stress in the Practice of Medicine.** 16 Cat 1 credit. Worcester. Info: Susan Lane, U of Massachusetts Medical School, Office of Cont Ed, 55 Lake Avenue North, Worcester, MA 01605. Tel: (617) 856-3041.

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THE MEDICAL SOCIETY
OF THE
STATE OF NEW YORK

invites nominations for the

Albert H. Douglas Memorial Award for Excellence in Clinical Teaching

The Douglas Award, consisting of a $500 stipend and a scroll, was established six years ago to honor outstanding clinical teachers in all branches of medicine. It is named for the late Dr. Douglas, who was a pioneer cardiologist and professor of clinical medicine at the State University of New York Stony Brook Medical Center.

Nominations are invited from undergraduate and graduate medical students and faculty. Names of candidates, along with substantiating material, should be sent to:

Committee on Awards and Prize Essays
Medical Society of the State of New York
420 Lakeville Road
Lake Success, NY 11042

The Deadline for submitting nominations is June 1, 1984.

MICHIGAN

Apr 12–13. **Institutional Ethics Committees and Healthcare Decisionmaking.** 5 Cat 1 credit. Detroit. Info: Conference Registrar, American Society of Law & Medicine, 765 Commonwealth Ave, Boston, MA 02215. Tel: (617) 262-4990.

NEBRASKA

Apr 9–14. **Emergency Medicine Review.** 45 Cat 1 credit. Omaha. Info: Marge Adey, Center for Cont Ed, U of Nebraska Medical Center, 42nd and Dewey, Omaha, NE 68105. Tel: (402) 559-4152.

NEW JERSEY

Apr 11. **The Sleepless Patient: Recent Clinical Advances.** 6 Cat 1 credit. Belle Mead. Info: Carolyn Shamy, c/o Sleep, Office of Med Ed, Carrier Foundation, Belle Mead, NJ 08502. Tel: (201) 874-4000, ext 461.

Apr 11–12. **Therapeutics in the 80's: A Critical Review.** 11.5 Cat 1 credit. Atlantic City. Info: Patricia Sarles, MS, UMDNJ-Office of Cont Ed, 100 Bergen St, Newark, NJ. Tel: (201) 456-4267.

TEXAS

Apr 6–7. **Cervical Neoplasia.** Houston. Info: Office of Conference Services, Box 131, MD Anderson Hospital and Tumor Institute, 6723 Bertner Ave, Houston, TX 77030. Tel: (713) 792-2222.

Apr 12. **Case Mix Payment—Impact and Challenge.** Dallas. Info: Continuing Education Services, 917 Pleasant Valley Blvd, Altoona, PA 16602. Tel: (814) 944-1535.

Apr 12–15. **Family Practice Recertification Review.** 24 Cat 1 credit. San Antonio, Info: U of Texas Health Science Center, 7703 Floyd Curl Drive, San Antonio, TX 78284. Tel: (512) 691-6295.

VIRGINIA

Apr 13–15. Emergency Medicine for the Primary Care Physician. 16.5 Cat 1 credit. Williamsburg. Info: Mrs Randy Casey, CME, Box 48 MCV Station, Richmond, VA 23298. Tel: (804) 786-0494.

1984 ANNUAL CME ASSEMBLY

PRESENTED BY THE

Medical Society of the State of New York

JUNE 29 - JULY 1

Sheraton Centre

Seventh Ave. & 52nd St.

New York City

◆

HIGHLIGHTS . . .

General Session: Medicine in this Age of Violence • 26 Sessions • Panel Discussions • Meet the Professor • Scientific & Technical Exhibits • Medical Society Reception

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Double/Twin	$88	$98	$114
Suite	$300 and Up		

Medical Society
of the
State of New York
June 29–July 1, 1984

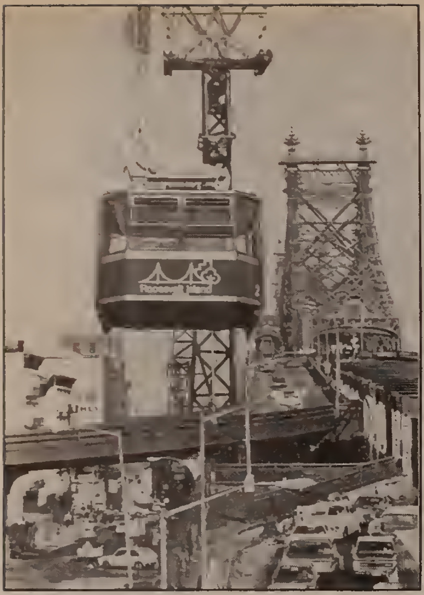
Reservations must be received by hotel no later than June 8.

IF RATE REQUESTED IS NOT AVAILABLE, NEXT AVAILABLE RATE WILL APPLY, RESERVATIONS RECEIVED AFTER SPECIFIED DATE WILL BE ACCOMMODATED ON A RATE AND SPACE AVAILABILITY BASIS ONLY.

Checkout time is 1:00 p.m. Normal Check in time is after 3:00 p.m.

Reservations are held until 6:00 p.m. unless guaranteed by a one nights deposit or guaranteed with one of the following credit cards: Diners Club, Carte Blanche, American Express.

Credit Card # ____________________ Exp. date ____________ Type ____________



General Information

Our CME Sessions are open to all physicians and the allied professions. The three full days of meetings will provide the individual physician with a possible 25 credits out of a total of 100, Category 1, CME credit hours being offered. Over 120 outstanding speakers, including a number from out-of-state, will present papers at 26 sessions. A highlight of the Assembly will be a general session on "Medicine in this Age of Violence," to be presented on Saturday, June 30th. Some areas to be discussed will be violence on the highway, in sports, in institutions, in war, sexual abuse of children, and drug abuse in adolescents.

Returning by popular request, "Meet the Professor" sessions will take place on Friday, June 29th. There will be six, 1½ hour sessions scheduled throughout the day.

Our program covers a wide range of medical specialties and focuses on helping the practicing physician meet the daily needs of patient care. You can be assured of an interesting program.

In addition, there will be Scientific and Technical Exhibits on display to update the physician on developments in both areas. Complimentary coffee breaks will be scheduled in the mornings and afternoons to allow time for physicians to visit the exhibits.

A reception for physicians and exhibitors, compliments of the Medical Society of the State of New York, will be held on Friday, June 29, from 6-7 pm. As the Assembly date closely precedes the 4th of July, we suggest that you bring your family to enjoy a pre-holiday weekend in New York City before continuing to your destination. The Sheraton Centre provides valet parking for your convenience.

Among the many new attractions in New York City are the downtown *South Street Seaport Museum,* a restoration of the early 19th century seaport that was engaged in trade and commerce. Here we find historic sailing ships at Pier 16, a multi-screen movie presentation of the early trading days, the Fulton Market with its restaurants, cafes, food shops, plus many specialty shops in the area. Uptown on Fifth Ave., the new *Trump Tower* presents a breathtaking, multilevel atrium lobby lined in pink marble, waterfalls and tropical plants. Escalators take you to international shops on each level. Visit the legendary WWII Aircraft Carrier *Intrepid, Sea-Air Space Museum* at Pier 86, a must experience for the entire family. Bring your family and join your colleagues for a weekend of stimulating CME sessions.

HOTEL RESERVATIONS

Physicians must make their own hotel reservation no later than June 8, 1984. If making reservations by telephone, please identify the Medical Society meeting for the special rate to apply.

REGISTRATION

Registration will take place in the Exhibition Centre, located on the lower level of the hotel. For those who registered in advance, your ID Badge will be held at the Medical Society Registration Desk. All new registrants must present identification at the registration desk.

REGISTRATION HOURS

Friday & Saturday —
8:30 a.m.-5:00 p.m.
Sunday — 8:30 a.m.-4:30 p.m.

MEETING HOURS

Friday — Meet the Professor,
8:30 a.m.-5:30 p.m.
All other meetings,
9:00 a.m.-5:00 p.m.
Saturday & Sunday —
9:00 a.m.-5:00 p.m.

1984 ANNUAL CME ASSEMBLY

Medical Society of the State of New York
Sheraton Centre, New York City

FRIDAY, JUNE 29

Morning	Cardiovascular Diseases, Royal Ballroom A Cancer Update, Versailles Terrace Pediatrics/School Health, Royal Ballroom B (all day) Meet the Professor, Consulate Suite Regency Foyer
Afternoon	Pediatrics/School Health, Royal Ballroom B Neurosurgery, Versailles Terrace Medical Legal & Workers' Compensation/Occupational Medicine, Royal Ballroom A Neurology, Regency Ballroom Meet the Professor, Consulate Suite Regency Foyer

SATURDAY, JUNE 30

Morning	Chest Diseases, Regency Ballroom Internal Medicine, Georgian Ballroom A (all day) Ophthalmology, Royal Ballroom A (all day) General Session "Violence", Georgian Ballroom B (all day) Obstetrics/Gynecology, Versailles Terrace Hand Surgery, Royal Ballroom B (all day)
Afternoon	Internal Medicine, Georgian Ballroom A Ophthalmology, Royal Ballroom A General Session "Violence", Georgian Ballroom B Dermatology/Otolaryngology, Versailles Terrace Pathology/Gastroenterology, Regency Ballroom Hand Surgery, Royal Ballroom B

SUNDAY, JULY 1

Morning	Allergy & Immunology, Georgian Ballroom A Family Practice/Preventive Medicine/Psychiatry, Royal Ballroom B (all day) Orthopedic Surgery/General Surgery/Plastic Surgery/Physical Medicine & Rehabilitation/Radiology/Anesthesiology, Georgian Ballroom B (all day) Urology/Emergency Medicine, Royal Ballroom A Women's Medical Society of New York State, Versailles Terrace
Afternoon	Family Practice/Preventive Medicine/Psychiatry, Royal Ballroom B Orthopedic Surgery/General Surgery/Plastic Surgery/Physical Medicine & Rehabilitation/Radiology/Anesthesiology, Georgian Ballroom B Alcoholism, Royal Ballroom A

□

CME CREDITS: Each program will be eligible for CME Category 1 credits on an hour-for-hour basis.

□

Technical & Scientific Exhibits

Note: The Preliminary Program will appear in the April issue.

Advance Registration Form

Complete and return this form to the Medical Society address as indicated below.

1984 Annual CME Assembly, June 29–July 1

SHERATON CENTRE, NEW YORK CITY

PLEASE PRINT

Name ____
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Address ____

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Please check category

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☐ Non-member physician	$50.00	
☐ Allied Profession	$10.00	

Please check category

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- ☐ Physician Assistant
- ☐ Dentist
- ☐ Lab Technician
- ☐ PT/OT
- ☐ Medical Writer
- ☐ Other (Specify) ______________

NO FEE

- ☐ Speaker
- ☐ Medical Student
- ☐ Medical Assistant
- ☐ Resident/Intern
- ☐ Spouse/Family
- ☐ News Media

MEET THE PROFESSOR

Friday, June 29th only. Fee: $25.00 per session. Please indicate session(s) attending. The six, 1½ hour sessions are limited to 30 persons each.

- ☐ 8:30 a.m. – Stephen Scheidt, M.D.
- ☐ 10:00 a.m. – Richard Gorlin, M.D.
- ☐ 11:30 a.m. – Howard Spiro, M.D.
- ☐ 1:00 p.m. – Eli Friedman, M.D.
- ☐ 2:30 p.m. – Philip Felig, M.D.
- ☐ 4:00 p.m. – Harold Neu, M.D.

(See this issue for subjects to be presented by each Professor)

REMITTANCE

Registration Fee $ ______________
Meet the Professor session(s) $ ______________
TOTAL $ ______________

Please make check payable to:
Medical Society of the State of New York, and return this form with remittance to: Division of Meeting Services, MSSNY, 420 Lakeville Rd., P.O. Box 5404, Lake Success, N.Y. 11042.

Important: Your ID Badge will be held at the MSSNY Registration Desk located in the Exhibition Centre, lower level, Sheraton Centre.

Meet the Professor — JUNE 29th

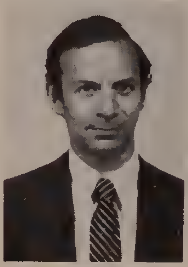
at the Medical Society of the State of New York's Annual CME Assembly, June 29-July 1, Sheraton Centre, New York City. Three sessions, 1½ hours each, will be offered on Friday morning, and three on Friday afternoon. Sessions are limited to 30 attendees each, and there is a $25.00 fee per session. Please see the registration form on the facing page.

Felig

Friedman

Gorlin

Neu


Scheidt

Spiro

Philip Felig, M.D.

Professor of Medicine & Chief of Endocrinology, Yale University School of Medicine, New Haven, Connecticut. This session will deal with newer intensive approaches to the management of diabetes, including self-monitoring of blood glucose, multiple insulin injections and insulin pump therapy.

Eli A. Friedman, M.D.

Professor of Medicine, Chief, Division of Renal Disease, SUNY Downstate Medical Center, Brooklyn, N.Y. Uremia therapy is one of the great successes of this century. There are currently more than 250,000 patients sustained by maintenance hemodialysis, peritoneal dialysis, and renal transplantation. The importance of identification and appropriate preparation of candidates for these therapies is self evident. The major causes of renal failure, its conservative management, and the advantages and problems of each therapeutic option will be considered.

Richard Gorlin, M.D.

Professor & Chairman of Medicine, Mount Sinai Hospital, New York City. The causes of heart failure and certain compensatory mechanisms which are called into play to abate it, in relation to chronic heart failure.

Harold Neu, M.D.

Professor of Medicine & Pharmacology, & Chief, Division of Infectious Diseases, Columbia University College of Physicians & Surgeons, New York City. This lecture will attempt to place all of the cephalosporin antibiotics in perspective so that the practicing physician will know when to use these drugs.

Stephen Scheidt, M.D.

Professor of Clinical Medicine, New York Hospital-Cornell Medical Center, New York City. To update the practicing physician on current knowledge concerning calcium blockers, including new data on arrhythmias, vasospastic angina, chronic stable angina, IHSS, hypertension, and other current or potential indications for their use.

Howard M. Spiro, M.D.

Professor of Medicine, Yale University School of Medicine, New Haven, Connecticut. Update the practicing physician on clinical and technological advances in gastroenterology while keeping the patient's problem as a focus.

Gene Luttenberg

Weekend Sightseeing for the Family

During the CME Assembly, June 29–July 1

SOUTH STREET SEAPORT & LOWER NEW YORK

New York's newest place to be is just a few blocks south of the Brooklyn Bridge, on Manhattan's lower eastern waterfront. It's an 11-block historic district, where in the year 1633, this area was the center of New Amsterdam's mercantile activity. By 1800, its port had surpassed both Boston and Philadelphia's to become the busiest in America. It continued to be an active port for the tall sailing ships until the late nineteenth century when steam ships replaced the sail. Today the area is being preserved and many of the buildings and ships have undergone restoration.

PHOTOS COURTESY N.Y. CONVENTION & VISITORS BUREAU

THE MUSEUM BLOCK

These beautifully restored buildings reflect 200 years of construction and architectural styles. The South Street Seaport Museum office building is believed to be the oldest, constructed in 1797. The Fish Building, built in 1914, is now the Trans-Lux Seaport Theater, with a multi-screen recreation of South Street's heyday. There are 17 shops in Museum Block, including Caswell-Massey, apothecary to George Washington, Blunt's Book & Chart Store which stocks nautical books and charts, the Seaport Gallery which displays ship models, a toy store, apparel shops, and an Italian restaurant.

FULTON MARKET

The original Fulton Market, built in 1822, housed butchers, fish merchants, and produce purveyors. Today, occupying a full block, it has been rebuilt to blend with the architecture of the neighborhood. It offers three exciting floors of restaurants, cafes, and specialty food shops. On the ground floor you can buy coffee, tea, cheese, fresh vegetables and fruits, fresh fish, kitchen accessories, bread and pastry, and you may dine at the sidewalk tables of an American restaurant. On the second level are 22 separate food stalls representing every type of cuisine. On the third floor you will find an elegant restaurant with an outdoor balcony overlooking the seaport.

SCHERMERHORN ROW

Named after the shipowner and merchant, Peter Schermerhorn, this row of late Georgian-Federal commercial buildings was built in 1812. The building provided office space for counting houses, housed seamen, sail makers and other merchants. The row of 12 buildings facing the gray cobblestones of Fulton Street has been cleaned and restored. Today we find an English Pub restaurant, seafood restaurants, marine antiques, and apparel shops.

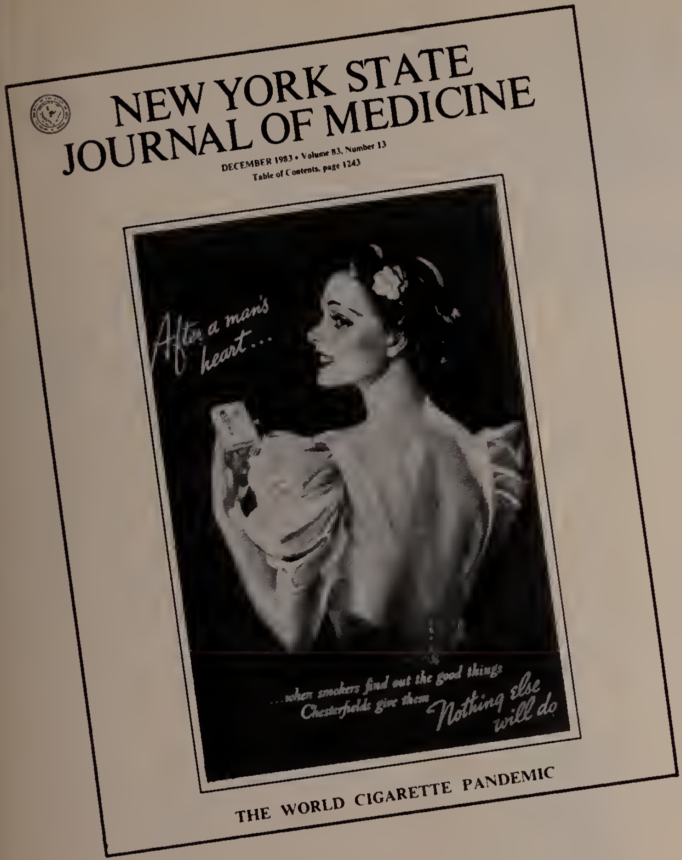
PIERS 15 AND 16

Here you may view the six moored ships. The four-masted steel bark *Peking* is one of the largest and last sailing ships built for commercial purposes. Built in 1911, she carried nitrate and fertilizer from South America to Europe. The *Wavertree,* an 1884 British full-rigged ship, built for the jute trade between India and Europe, was dismasted off Cape Horn in 1910. Also, you may view the *Ambrose* lightship built in 1907 to mark the entrance to Ambrose Channel in New York Harbor. Other vessels on view are the *Pioneer,* launched as a sloop in 1885 and later restored as a gaff-rigged schooner, plus the *Lettie G. Howard,* a Glaucester schooner built in 1893.

GRAY LINE TOURS

Doctor, we recommend that you bring your family to New York City in June where you may attend meetings at the CME Assembly and also join your family in a tour of the South Street Seaport. The Gray Line offers guided tours of lower New York and the South Street Seaport (Tour #7), and has five hourly departures daily from 9:00 a.m. to 1:00 p.m. In addition to the South Street Seaport, the tour includes views of several squares, including Washington Square, continuing to Chinatown, the Civic Center, the financial and maritime districts, Battery Park, the World Trade Center, and a ride along the East River past the U.N. to Rockefeller Center.

The tour #7 lasts about 5½ hours and departs and returns to the Gray Line terminal located at 8th Avenue and 54th Street, just two blocks from the Sheraton Centre Hotel. The tour price is $19.50, and tickets may be purchased at the theatre/tour desk in the lobby of the Sheraton Centre Hotel.



NEW YORK STATE JOURNAL OF MEDICINE

DECEMBER 1983 • Volume 83, Number 13

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THE WORLD CIGARETTE PANDEMIC

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NOTICES

Peter Rogatz, MD, MPH, has been appointed Vice President for Medical Affairs of the Visiting Nurse Service of New York. His responsibilities include serving as the medical director for the agency's extended care program for dying patients and their families, overseeing utilization review for the agency's home care program, and maintaining liaison between home care staff and physicians in the community.

Lenox Hill Hospital in Manhattan has appointed Michael R Sanders, MD, as Director of the Hemodynamics Laboratory, Department of Medicine, and Stephen C Scharf, MD, as Chief of the Nuclear Medicine Section, Department of Radiology.

Gerald R Cooper, MD, Medical Officer of the Clinical Chemistry Division of the Centers for Disease Control in Atlanta, GA, and Medical Director of the World Health Organization's Center for Research and Services in Blood Lipids, was elected President of the American Association for Clinical Chemistry.

The Greater New York Hospital Foundation has received a $17,500 grant from the United Hospital Fund in support of a special study designed to analyze the characteristics of patients seeking care in hospital walk-in facilities, the causes of such visits, and the source of payments. The information will be used in an effort to improve health care policy making.

Drew Gaffney, MD, assistant professor of internal medicine at The University of Texas Health Science Center at Dallas has been selected to be a payload specialist on an upcoming NASA Space Shuttle mission in January. In this role, Dr Gaffney, whose research interest is adaptation of the heart and lungs to the weightless condition of space, will perform a series of more than 20 experiments in human and animal physiology and plant adaptation.

John Naughton, MD, dean of the medical school and acting vice president of health sciences at the State University of New York at Buffalo, has been appointed to the executive committee of the Council of Deans of the Association of American Medical Colleges.

References:
1. Stone PH, Turi ZG, Muller JE: Efficacy of nifedipine therapy for retractory angina pectoris. *Am Heart J* 104:672-681, September 1982.
2. Antman E, Muller J, Goldberg S, et al: Nifedipine therapy for coronary-artery spasm: Experience in 127 patients. *N Engl J Med* 302:1269-1273, June 5, 1980.

BRIEF SUMMARY
PROCARDIA® (nifedipine) **CAPSULES** For Oral Use

INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is retractory to nitrates and/or adequate doses of beta blockers

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in those patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See Warnings.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving PROCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PROCARDIA and a beta blocker, but the possibility that it may occur with PROCARDIA alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In PROCARDIA treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for PROCARDIA to be washed out of the body prior to surgery.

Increased Angina: Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Beta Blocker Withdrawal: Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients, usually receiving a beta blocker, have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See Warnings.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Drug Interactions: Beta-adrenergic blocking agents: (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing PROCARDIA to avoid possible over- or under-digitalization.

Carcinogenesis, mutagenesis, impairment of fertility: When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose

Pregnancy: Category C. Please see full prescribing information with reference to teratogenicity in rats, embryotoxicity in rats, mice and rabbits, and abnormalities in monkeys.

ADVERSE REACTIONS: The most common adverse events include dizziness or light-headedness, peripheral edema, nausea, weakness, headache and flushing each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5% Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication Additionally, the following have been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, diarrhea, constipation, inflammation, joint stiffness, shakiness, sleep disturbances, blurred vision, difficulties in balance, dermatitis, pruritus, urticaria, fever, sweating, chills, and sexual difficulties. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

Laboratory Tests: Rare, mild to moderate, transient elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted, and a single incident of significantly elevated transaminases and alkaline phosphatase was seen in a patient with a history of gall bladder disease after about eleven months of nifedipine therapy The relationship to PROCARDIA therapy is uncertain. These laboratory abnormalities have rarely been associated with clinical symptoms. Cholestasis, possibly due to PROCARDIA therapy, has been reported twice in the extensive world literature

HOW SUPPLIED: Each orange, soft gelatin PROCARDIA CAPSULE contains 10 mg of nifedipine PROCARDIA CAPSULES are supplied in bottles of 100 (NDC 0069-2600-66), 300 (NDC 0069-2600-72), and unit dose (10x10) (NDC 0069-2600-41). The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

More detailed professional information available on request. © 1982, Pfizer Inc

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"I can do things that I couldn't do for 3 yrs. including joining the human race again."

Quotes from an unsolicited letter received by Pfizer from an angina patient
While this patient's experience is representative of many unsolicited comments received, not all patients will respond to Procardia nor will they all respond to the same degree.

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"My daily routine consisted of sitting in my chair trying to stay alive."

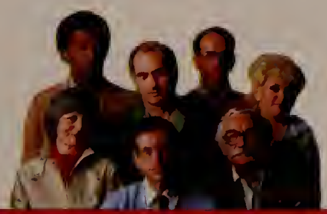
"My doctor switched me to PROCARDIA[*] *as soon as it became available. The change in my condition is remarkable."*

"I shop, cook and can plant flowers again."

"I have been able to do volunteer work...and feel needed and useful once again."

PROCARDIA can mean the return to a more normal life for your patients—having fewer anginal attacks,[1] taking fewer nitroglycerin tablets,[2] doing more, and being more productive once again.

Side effects are usually mild (most frequently reported are dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%).



for the varied faces of angina

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*Procardia is indicated for the management of:
1) Confirmed vasospastic angina.
2) Angina where the clinical presentation suggests a possible vasospastic component.
3) Chronic stable angina without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or nitrates or who cannot tolerate these agents. In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks' duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

Please see PROCARDIA *brief summary on adjoining page.*

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MISCELLANEOUS—CONT'D

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PROFESSIONAL CONDUCT EXPERT. Robert S. Asher, J.D., M.P.A., in health, former Director Professional Conduct, N.Y.S. Board of Regents, now in private legal practice. 15 years health law experience concentrating on professional practice, representation before government agencies on Disciplinary, Licensure, Narcotic Control, Medicaid, Medicare of Third-Party Reimbursement matters and professional business practice. Robert S. Asher, Esq., 110 E. 42nd Street, NYC. (212) 697-2950 or evenings (914) 723-0799.

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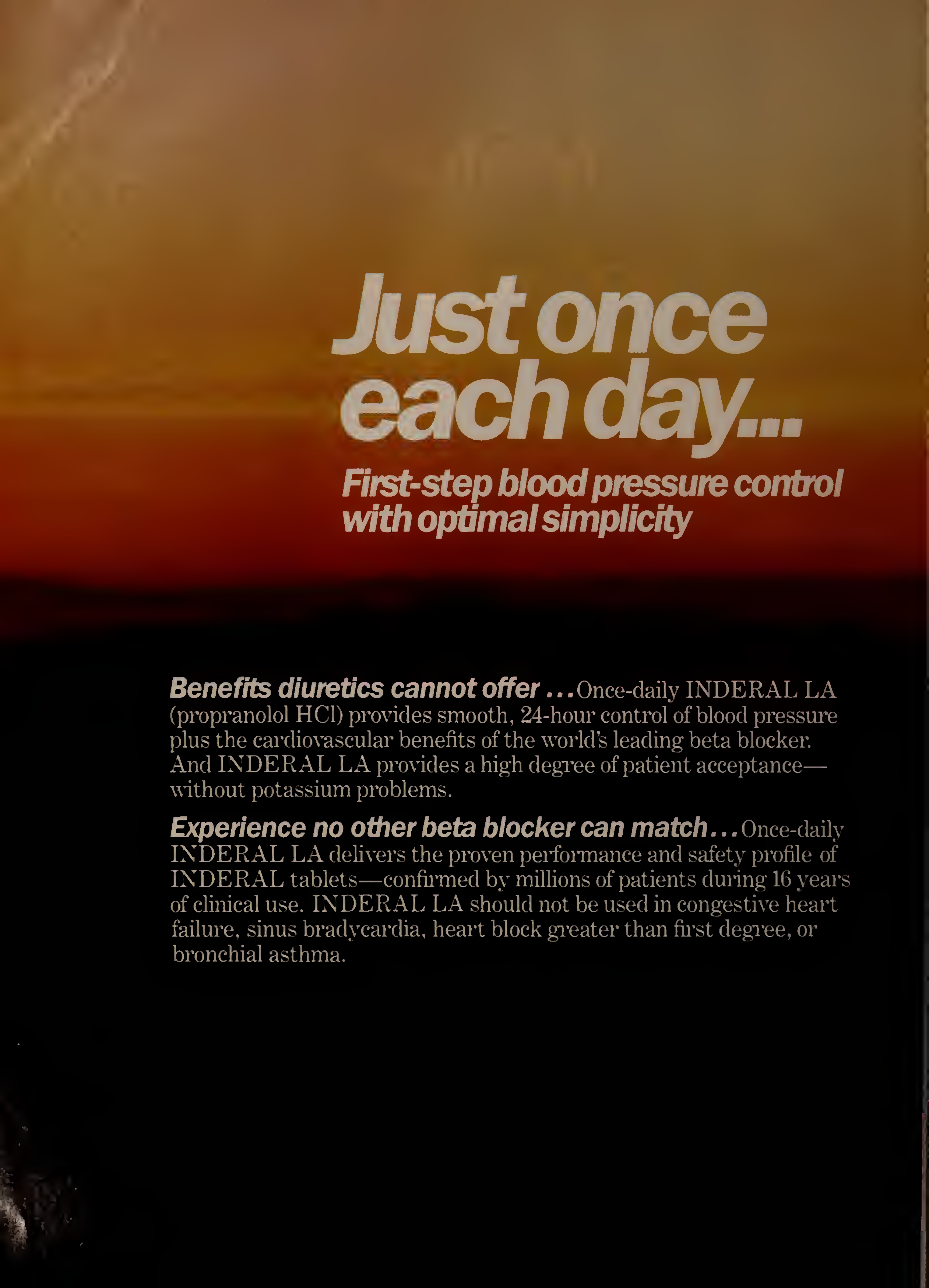

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Start with 80 mg once daily… Dosage may be increased to 120 mg or 160 mg once daily as needed to achieve additional control. Please see next page for further details and brief summary of prescribing information.

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INDERAL LA

(PROPRANOLOL HCl) LONG-ACTING CAPSULES

Just once each day for initial therapy in hypertension.

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Just once each day for initial therapy in HYPERTENSION.

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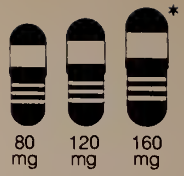

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)*
INDERAL® LA brand of propranolol hydrochloride **(Long Acting Capsules)**
DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.
CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and [illegible]ewhat variable. INDERAL has been shown to cause a small increase in serum potassi[illegible] concentration when use[illegible] the treatment of hypertensive patients

In angina pectoris, propranolol generally reduces th[illegible]n re[illegible]t any given level of effort by blocking the catecholamine[illegible] inc[illegible] the h[illegible] rate, systolic blood pressure, and the velocity and extent of [illegible]rdial [illegible]nolol may increase oxygen requirements by increasing left [illegible]lar f[illegible] length, [illegible]stolic pressure and systolic ejection period The net phy[illegible]ene[illegible]de is usually advantageous and is manifested duri[illegible]rcis[illegible]t [illegible]nd increased work capacity.

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-[illegible] or anesthetic-like membrane action which affects th[illegible]c a[illegible]nti[illegible]ig[illegible] cance of the membrane action in the treatment of [illegible]ythm[illegible] i[illegible] cen[illegible]

The mechanism of the antimigraine effect of pr[illegible]anolol [illegible]lished. B[illegible]-adrenergic receptors have been demonstrated in [illegible] pial vess[illegible] of the [illegible]

Beta receptor blockade can be useful in con[illegible]ns in [illegible] beca[illegible] path[illegible]r functional changes, sympathetic activity is detri[illegible]o situations in which sympathetic stimulation is vital [illegible]xampl[illegible], in patients [illegible] severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable
INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary
CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first degree block; 3) bronchial asthma; 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL
WARNINGS. CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible)

> IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

Just once each day...

MAJOR SURGERY The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA. Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol
PRECAUTIONS. *General:* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in [illegible] rats [illegible] emplo[illegible] doses [illegible] 150 mg/kg/day, there was no evidence of significant [illegible]lated tumorigenic effects at any of the dosage level[illegible]duc[illegible]dies [illegible]mals [illegible] not show any impairment of fertility that was attri[illegible] to th[illegible]

[illegible]ncy [illegible]ncy Cat[illegible]ry C [illegible]DERAL has been shown to be embryotoxic in [illegible]ies a[illegible]er than the maximum recommended human dose

Th[illegible] are n[illegible]eq[illegible]d w[illegible]olled studies in pregnant women. INDERAL should be used during p[illegible]gnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mot[illegible]s. INDERAL is excreted in human milk Caution should be exercised when [illegible]DERAL [illegible]dm[illegible]ste[illegible] a [illegible]rsing w[illegible]an.

Pe[illegible]ric [illegible]ely a[illegible]ctive[illegible]ss in children have not been established
[illegible]DVE[illegible]SE R[illegible]CTIONS. [illegible] adv[illegible]se effects have been mild and transient and have [illegible]rely [illegible]quired [illegible]draw[illegible] of [illegible]er[illegible]

C[illegible]diovas[illegible] brady[illegible]dia[illegible]ngestive heart failure; intensification of AV block, hypo-[illegible]ensio[illegible] thr[illegible]bo[illegible]urpura, arterial insufficiency, usually of the [illegible]aynaud type.

Central Nervous System [illegible]headedness, mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia, visual disturbances, hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported

Miscellaneous. alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.
DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved The usual maintenance dosage is 120 to 160 mg once daily In some instances a dosage of 640 mg may be required The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS)

MIGRAINE—*Dosage must be individualized* The initial oral dose is 80 mg INDERAL LA once daily The usual effective dose range is 160-240 mg once daily The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued It may be advisable to withdraw the drug gradually over a period of several weeks

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily
PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

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- More total sleep time[1-6]
- Undiminished efficacy for at least 28 consecutive nights[2-4]
- Patients usually awake rested and refreshed[7-9]
- Avoids causing early awakenings or rebound insomnia after discontinuation of therapy[2,5,10-12]

Caution patients about driving, operating hazardous machinery or drinking alcohol during therapy. Limit dose to 15 mg in elderly or debilitated patients. Contraindicated during pregnancy.

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References: **1.** Kales J *et al*: *Clin Pharmacol Ther* *12*:691-697, Jul-Aug 1971. **2.** Kales A *et al*: *Clin Pharmacol Ther 18*:356-363, Sep 1975. **3.** Kales A *et al*: *Clin Pharmacol Ther 19*:576-583, May 1976. **4.** Kales A *et al*: *Clin Pharmacol Ther 32*:781-788, Dec 1982. **5.** Frost JD Jr, DeLucchi MR: *J Am Geriatr Soc 27*:541-546, Dec 1979. **6.** Kales A, Kales JD: *J Clin Pharmacol 3*:140-150, Apr 1983. **7.** Greenblatt DJ, Allen MD, Shader RI: *Clin Pharmacol Ther 21*:355-361, Mar 1977. **8.** Zimmerman AM: *Curr Ther Res 13*:18-22, Jan 1971. **9.** Amrein R *et al*: *Drugs Exp Clin Res* 9(1):85-99, 1983. **10.** Monti JM: *Methods Find Exp Clin Pharmacol 3*:303-326, May 1981. **11.** Greenblatt DJ *et al*: *Sleep* 5(Suppl 1):S18-S27, 1982. **12.** Kales A *et al*: *Pharmacology 26*:121-137, 1983.

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Before prescribing, please consult complete product information, a summary of which follows:

Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; in acute or chronic medical situations requiring restful sleep. Objective sleep laboratory data have shown effectiveness for at least 28 consecutive nights of administration. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended. Repeated therapy should only be undertaken with appropriate patient evaluation.

Contraindications: Known hypersensitivity to flurazepam HCl; pregnancy. Benzodiazepines may cause fetal damage when administered during pregnancy. Several studies suggest an increased risk of congenital malformations associated with benzodiazepine use during the first trimester. Warn patients of the potential risks to the fetus should the possibility of becoming pregnant exist while receiving flurazepam. Instruct patient to discontinue drug prior to becoming pregnant. Consider the possibility of pregnancy prior to instituting therapy.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. An additive effect may occur if alcohol is consumed the day following use for nighttime sedation. This potential may exist for several days following discontinuation. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Potential impairment of performance of such activities may occur the day following ingestion. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, abrupt discontinuation should be avoided with gradual tapering of dosage for those patients on medication for a prolonged period of time. Use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in severely depressed patients, or in those with latent depression or suicidal tendencies, or in those with impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins, and alkaline phosphatase; and paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity.

Dosage: Individualize for maximum beneficial effect. *Adults:* 30 mg usual dosage; 15 mg may suffice in some patients. *Elderly or debilitated patients:* 15 mg recommended initially until response is determined.

Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.

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flurazepam HCl/Roche

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15-MG/30-MG CAPSULES

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NEW YORK STATE JOURNAL OF MEDICINE

APRIL 1984 • Volume 84, Number 4

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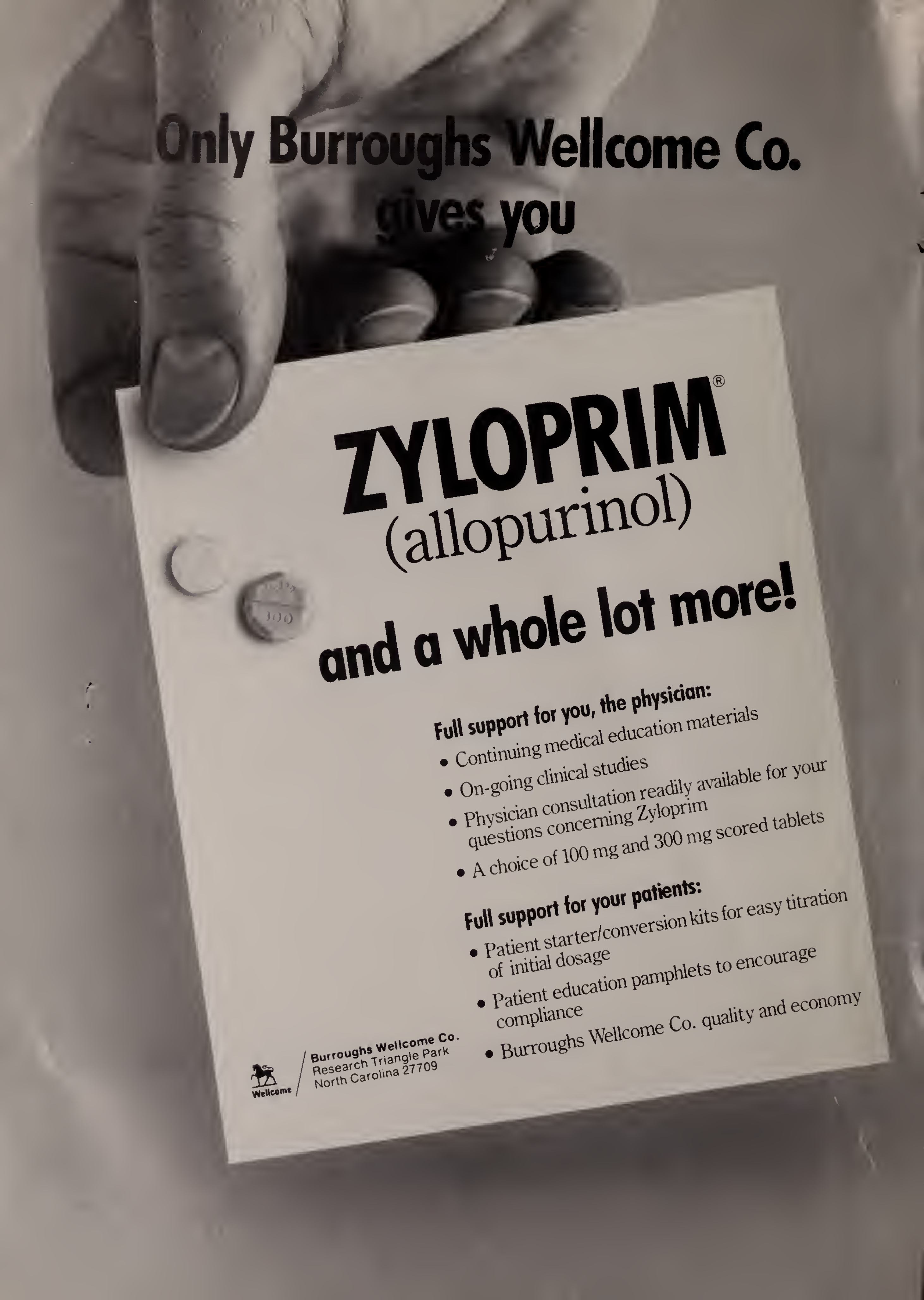

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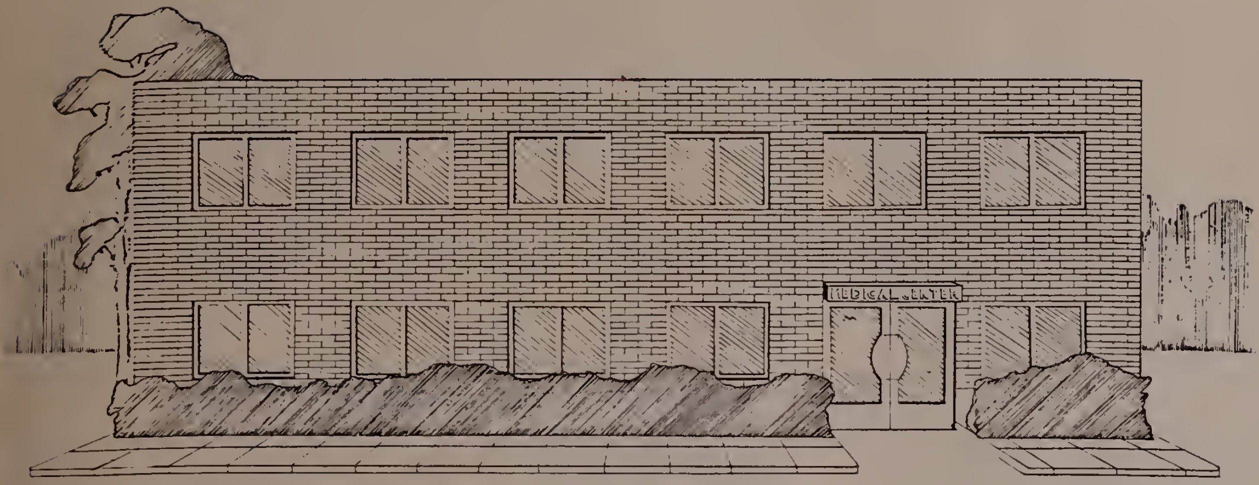

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Start with 80 mg once daily… Dosage may be increased to 120 mg or 160 mg once daily as needed to achieve additional control. Please see next page for further details and brief summary of prescribing information.

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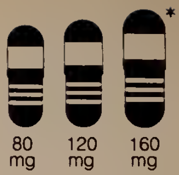

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)*
INDERAL® LA brand of propranolol hydrochloride **(Long Acting Capsules)**

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CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

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In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity.

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain.

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block; 3) bronchial asthma; 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS. CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

> IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. *General:* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block, hypotension; paresthesia of hands; thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia, visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized.* The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily.

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

*The appearance of INDERAL LA capsules is a registered trademark of Ayerst Laboratories.

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CARDIOLOGY PRACTICE Available: Upstate New York. Solo practice with coverage; swanz-ganz, stress lab, pacemakers; 12-bed ICU/CCU, CT scanner, nuclear medicine. Community hospital located one hour from major city with access to water and mountains. Large service area. Substantial practice income guarantee available and first year office rent paid. Send CV in confidence to: P.O. Box 7436, FDR Station, New York, N.Y. 10150.

References:

1. Stone PH, Turi ZG, Muller JE: Efficacy of nifedipine therapy for refractory angina pectoris. *Am Heart J* 104:672-681, September 1982.
2. Antman E, Muller J, Goldberg S, et al: Nifedipine therapy for coronary-artery spasm: Experience in 127 patients. *N Engl J Med* 302:1269-1273, June 5, 1980

BRIEF SUMMARY
PROCARDIA® (nifedipine) **CAPSULES** For Dral Use

INDICATIDNS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PRDCAROIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PRDCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in those patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See Warnings.)

CDNTRAINDICATIDNS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving PRDCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PROCARDIA and a beta blocker, but the possibility that it may occur with PROCAROIA alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In PROCARDIA treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for PROCARDIA to be washed out of the body prior to surgery.

Increased Angina: Dccasional patients have developed well documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Beta Blocker Withdrawal: Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCAROIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients, usually receiving a beta blocker, have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See Warnings.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Drug Interactions: Beta-adrenergic blocking agents: (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing PROCARDIA to avoid possible over- or under-digitalization.

Carcinogenesis, mutagenesis, impairment of fertility: When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose

Pregnancy: Category C. Please see full prescribing information with reference to teratogenicity in rats, embryotoxicity in rats, mice and rabbits, and abnormalities in monkeys.

ADVERSE REACTIDNS: The most common adverse events include dizziness or light-headedness, peripheral edema, nausea, weakness, headache and flushing each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5% Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Additionally, the following have been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, diarrhea, constipation, inflammation, joint stiffness, shakiness, sleep disturbances, blurred vision, difficulties in balance, dermatitis, pruritus, urticaria, fever, sweating, chills, and sexual difficulties. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

Laboratory Tests: Rare, mild to moderate, transient elevations of enzymes such as alkaline phosphatase, CPK, LOH, SGOT, and SGPT have been noted, and a single incident of significantly elevated transaminases and alkaline phosphatase was seen in a patient with a history of gall bladder disease after about eleven months of nifedipine therapy. The relationship to PROCARDIA therapy is uncertain. These laboratory abnormalities have rarely been associated with clinical symptoms. Cholestasis, possibly due to PROCARDIA therapy, has been reported twice in the extensive world literature

HOW SUPPLIED: Each orange, soft gelatin PROCAROIA CAPSULE contains 10 mg of nifedipine PROCAROIA CAPSULES are supplied in bottles of 100 (NOC 0069-2600-66), 300 (NOC 0069-2600-72), and unit dose (10x10) (NDC 0069-2600-41). The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

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"I can do things that I couldn't do for 3 yrs. including joining the human race again."

"My daily routine consisted of sitting in my chair trying to stay alive."

"My doctor switched me to PROCARDIA[*] *as soon as it became available. The change in my condition is remarkable."*

"I shop, cook and can plant flowers again."

"I have been able to do volunteer work...and feel needed and useful once again."

PROCARDIA can mean the return to a more normal life for your patients—having fewer anginal attacks,[1] taking fewer nitroglycerin tablets,[2] doing more, and being more productive once again.

Side effects are usually mild (most frequently reported are dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%).

Quotes from an unsolicited letter received by Pfizer from an angina patient.
While this patient's experience is representative of many unsolicited comments received, not all patients will respond to Procardia nor will they all respond to the same degree.

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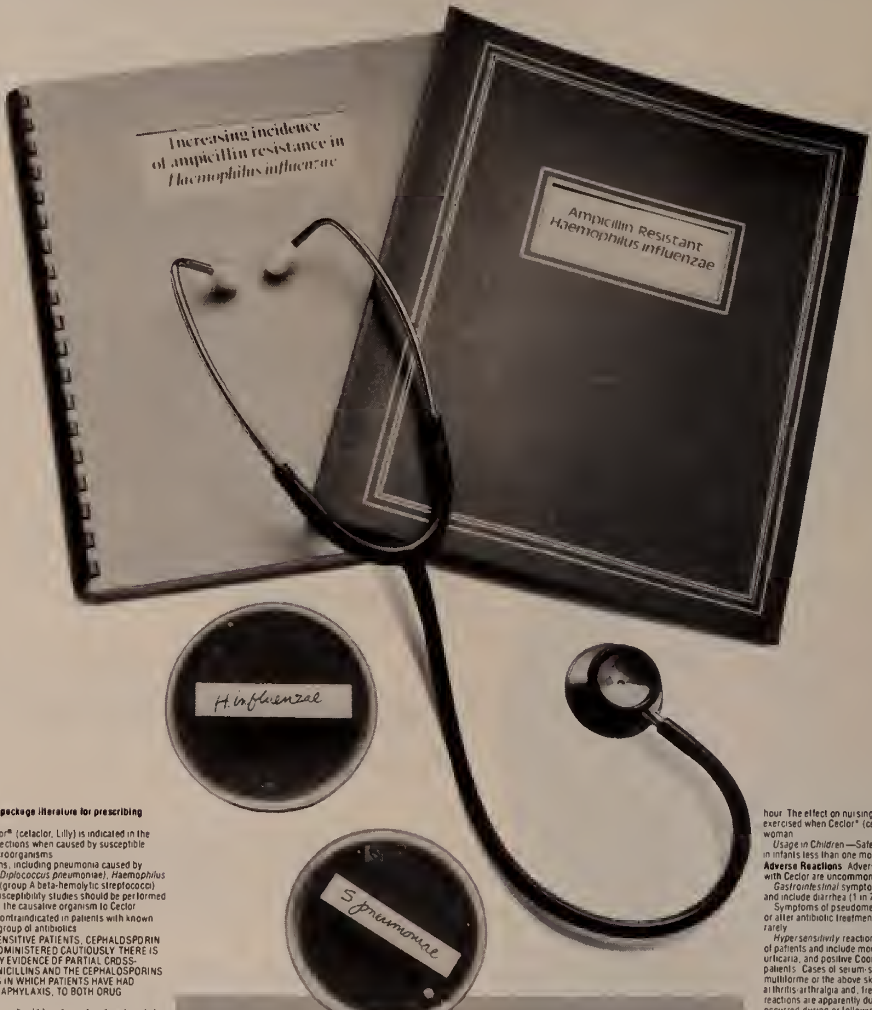
for the varied faces of angina

PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

*Procardia is indicated for the management of:
1) Confirmed vasospastic angina.
2) Angina where the clinical presentation suggests a possible vasospastic component.
3) Chronic stable angina without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or nitrates or who cannot tolerate these agents. In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks' duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

Please see PROCARDIA *brief summary on adjoining page.*

An added complication... in the treatment of bacterial bronchitis*


Increasing incidence of ampicillin resistance in Haemophilus influenzae
Ampicillin Resistant Haemophilus influenzae
H. influenzae
S. pneumoniae

Some ampicillin-resistant strains of Haemophilus influenzae—a recognized complication of bacterial bronchitis*—are sensitive to treatment with Ceclor.[1-6]

In clinical trials, patients with bacterial bronchitis due to susceptible strains of Streptococcus pneumoniae, H. influenzae, S. pyogenes (group A beta-hemolytic streptococci), or multiple organisms achieved a satisfactory clinical response with Ceclor.[7]

Ceclor®
cefaclor

Pulvules®, 250 and 500 mg

Brief Summary Consult the package literature for prescribing information.

Indications and Usage Ceclor® (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae (Diplococcus pneumoniae), Haemophilus influenzae*, and *S pyogenes* (group A beta-hemolytic streptococci)

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins), therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics Such colitis may range in severity from mild to life-threatening

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid electrolyte and protein supplementation When the colitis does not improve after the drug has been discontinued, or when it is severe oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by C *difficile* Other causes of colitis should be ruled out

Precautions *General Precautions*—If an allergic reaction to Ceclor occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents e g , pressor amines, antihistamines or corticosteroids

Prolonged use of Ceclor may result in the overgrowth of nonsusceptible organisms Careful observation of the patient is essential If superinfection occurs during therapy, appropriate measures should be taken

Positive direct Coombs tests have been reported during treatment with the cephalosporin antibiotics In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug

Ceclor should be administered with caution in the presence of markedly impaired renal function Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended

As a result of administration of Ceclor, a false positive reaction for glucose in the urine may occur This has been observed with Benedict s and Fehling s solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly)

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis

Usage in Pregnancy—Pregnancy Category B—Reproduction studies have been performed in mice and rats at doses up to 12 times the human dose and in ferrets given three times the maximum human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Ceclor There are however, no adequate and well-controlled studies in pregnant women Because animal reproduction studies are not always predictive of human response this drug should be used during pregnancy only if clearly needed

Nursing Mothers—Small amounts of Ceclor have been detected in mother s milk following administration of single 500-mg doses Average levels were 0 18 0 20, 0 21 and 0 16 mcg/ml at two, three four, and five hours respectively Trace amounts were detected at one hour The effect on nursing infants is not known Caution should be exercised when Ceclor® (cefaclor, Lilly) is administered to a nursing woman

Usage in Children—Safety and effectiveness of this product for use in infants less than one month of age have not been established

Adverse Reactions Adverse effects considered related to therapy with Ceclor are uncommon and are listed below

Gastrointestinal symptoms occur in about 2 5 percent of patients and include diarrhea (1 in 70)

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment Nausea and vomiting have been reported rarely

Hypersensitivity reactions have been reported in about 1 5 percent of patients and include morbilliform eruptions (1 in 100) Pruritus, urticaria, and positive Coombs tests each occur in less than 1 in 200 patients Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever) have been reported These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Ceclor Such reactions have been reported more frequently in children than in adults Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy. No serious sequelae have been reported Antihistamines and corticosteroids appear to enhance resolution of the syndrome

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients)

Causal Relationship Uncertain—Transitory abnormalities in clinical laboratory test results have been reported Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician

Hepatic—Slight elevations of SGOT, SGPT, or alkaline phosphatase values (1 in 40)

Hematopoietic—Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40)

Renal—Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200)

[061782R]

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*Many authorities attribute acute infectious exacerbation of chronic bronchitis to either *S pneumoniae* or *H influenzae* [8]

Note Ceclor is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever See prescribing information

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Carolina Puerto Rico 00630

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NEW YORK STATE
JOURNAL OF MEDICINE

April 1984 • Volume 84, Number 4

COMMENTARIES

A second look at the Pomeroy method of tubal sterilization

In 1930, in this journal, there appeared an article entitled "A simple method of tubal sterilization," written by Eliot Bishop, MD and William Nelms, MD,[1] obstetricians and gynecologists at The Brooklyn Hospital. In the article they described a technique for surgical sterilization performed by Ralph Pomeroy, MD, the late director of the department. They also reviewed the methods of tubal sterilization used at that time, noting the large numbers of failures that occurred and commenting that the material used in almost all these techniques was a non-absorbable suture. They emphasized that this procedure had the three principles that any surgical procedure should exhibit: simplicity, safety, and surety. Today, more than five decades later, the Pomeroy technique of tubal sterilization still fulfills these three principles.

Simplicity. Tubal sterilization is the second most common surgical procedure performed on women of reproductive age—more than 700,000 per year in the United States alone. The Pomeroy method, entailing a loop in the middle portion of the tube ligated with an absorbable suture and then resected, is a procedure readily mastered by the first-year resident in training. The introduction by Vitoon[2] in Thailand of the "minilap" has made the operation even shorter and simpler, capable of being performed under local anesthesia and leaving the patient with a cosmetically acceptable scar. In this procedure an intrauterine instrument is employed to elevate and manipulate the uterus from side to side. The minilap Pomeroy is especially useful in overweight patients, those with previous lower abdominal surgery, and those with major medical complications.

With the development of the laparoscope in the late 1960s, a significant alternative to sterilization by laparotomy became available. The last 10 years has seen a decreasing percentage of sterilizations performed by laparotomy and an increasing percentage first by laparoscopic electrocautery, and more recently by laparoscopic rings and clips. Technically the laparoscopic procedures are more difficult, require more training of personnel, and use sophisticated equipment that is subject to breakdown and expensive repair—factors that may be critical in underdeveloped countries.

Safety. Current methods of tubal sterilization are all relatively safe procedures, with four deaths per 100,000 tubal sterilizations in the United States each year. Forty percent of the deaths are due to problems with anesthesia, the remainder to infection and hemorrhage.[3] A study of more than 15,000 sterilizations by the International Fertility Research Association showed a surgical complication rate of 2.04 percent for the laparoscopic ring method and 0.79 percent for the minilap Pomeroy.[4] Not only were there more surgical complications with the former, but the types of complications were also more serious, including trocar injuries, complications of pneumoperitoneum and occlusion of structures other than the Fallopian tube.

In 1951 Williams[5] reported an increased incidence of menstrual disturbances in women who had undergone tubal sterilization. Other retrospective studies[6-8] have reported irregular and prolonged menstrual flow, pelvic pain, or both in 5–10 percent of women following tubal sterilization. It was postulated that the blood flow to the ovary might be compromised by the sterilization procedure, resulting in dysfunctional cycles. In 1983 two large prospective studies, one from Great Britain[9] and the other from the United States,[10] were published. The British study used women whose husbands had undergone vasectomy as controls; in the other study each woman served as her own control—her menstrual history prior to surgery was compared with her menstrual function two years after surgery. Both studies showed no significant increase in the incidence of adverse menstrual disorders following tubal sterilization, with the exception of an increase in menstrual pain among women who underwent unipolar electrocoagulation procedures.

Surety. Most studies show a subsequent pregnancy rate of 0.3 to 0.6 percent in the first year after tubal sterilization.

In the International Fertility Research study,[3] the failure rate for the laparoscopic ring procedure was twice as high as that for the minilap Pomeroy (0.6 to 0.3 percent). The prospective British study[8] showed the same percentage failure rate for each type of procedure, but the numbers were too small to achieve statistical significance.

Thus, more than fifty years after its initial description, the Pomeroy method of tubal sterilization has established itself worldwide as a simple, safe and sure procedure.

JOAN F. SPITALERI, MD
Co-director
Department of Obstetrics and Gynecology
The Brooklyn Hospital-Caledonian Hospital
121 DeKalb Avenue
Brooklyn, NY 11201

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Leboyer and obstetric practice

No one can question the observation that obstetrical practice has undergone dramatic change in recent years because of improved technology and heightened expectations for safe delivery. Electronic fetal monitoring, antenatal testing, and cesarean section have improved perinatal statistics. Smaller families and the availability of alternative approaches to childbirth increase the numbers of parents who demand to play a greater role in the delivery while at the same time expecting a more satisfying outcome. There is conflict implicit in these changes, for our technology has become complex at a time when patient expectations are often based on a view of childbirth as a process that they can participate in and control.

As an example of the swift and drastic changes in childbirth, I recall my own experiences as a resident during the early 1960s. "Twilight sleep" was in vogue, because it was thought that by removing the mother from the pain of the birth experience she would be a better parent.[1] Her amnesia for the birth experience was felt to be beneficial. In the 1960s there was no role for the father during childbirth; he was pictured as an indifferent, incompetent oaf, chain-smoking in the waiting room until someone remembered to tell him about the baby. The newborn was considered to be only an animated lump of flesh that was able to survive, but certainly had neither intelligence nor feelings. As a consequence, the mother and her baby were dehumanized, over-medicated, and separated from the father and the rest of the family—all, supposedly, to facilitate a "safe delivery."

It is predictable that, given this framework for care, the "natural" childbirth movement, as espoused by Dr Grantly Dick-Read[2] and others, would have tough sledding, and it did. There were marked philosophical differences between "natural childbirth" and the then current medical approach to the management of labor and delivery, particularly revolving around the use of medication and anesthesia. However, support began to develop, albeit reluctantly, when it was noted by Dr T. Berry Brazelton[3] that heavy sedative and narcotic or anesthetic agents had adverse depressive effects on the infant at birth. The Lamaze method and other approaches that helped to reduce the need for medications and anesthesia during labor and delivery were used in the 1970s. The father-attended birth movement, which we now readily appreciate, had a more difficult time gaining acceptance. Since feelings, rather than medication, were involved, it was harder to demonstrate a positive benefit with the father present at birth. Nonetheless, partially through consumer pressure, and partly because of changed perceptions by physicians themselves, fathers began to appear in delivery rooms by the mid-1970s, and family-centered care now is accepted across the country.

At the same time as our perceptions of the parents' experiences during birth were changing, our knowledge of infant behavior and intellectual capacity also was growing. Dr Lee Salk,[4] a child psychologist, and Dr Brazelton,[5] a pediatrician, through their observations of newborns affirmed that the human infant is a remarkably intelligent and perceptive person. Drs Marshall Klaus and John Kennel[6] reported their initial observations on the benefits of "maternal-infant bonding" during the puerperium. The family-oriented view of the childbirth drama, with the infant at the center of a "biopsychosocial" stage gained credence both with young parents-to-be and with many of the professionals caring for them.

Leboyer and his emotion-laden message[7] flashed across this sensitized scenario like a shooting star, awakening in couples many new expectations for childbirth and exposing physicians and nurse-midwives to new viewpoints and options. Although Leboyer appears to have just as quickly passed from our view, many behavior changes that he advocated have remained for us to accept or question. Surprisingly, many of these changes have crept into usage with little or no fanfare and with much acceptance by patient and staff. I began using a modified "Leboyer approach" after meeting him in 1975; the darkened delivery room, immediate skin-to-skin contact between the mother and the infant, and the warm water bath were incorporated into a family-centered experience. Parent-infant bonding was emphasized, and "high technology" de-emphasized for low-risk deliveries. Once one's eyes were dark adapted, an Apgar score can be obtained, and none of the predicted problems occurred. I have been impressed with the safety of these procedures in the years since I first used them, and am always thrilled by the heightened sense of satisfaction that both parents express with the birthing process. Many of my patients have remained personal friends, and still recall the importance to them of their birthing experiences, even after five or more years.

Whether or not there is a direct beneficial effect on the newborn or on parental behavior because of Leboyer modifications in our approach to labor and delivery awaits discovery through more perceptive and long-term studies. The studies of Rapoport[8] were hopeful, but lacked adequate controls. The report of Nelson and Enkin et al[9] did not extend over a long enough period to be convincing, while it did demonstrate that many Leboyer modifications are already being incorporated into regular practices. The study reported by Kliot[10] in this issue makes no attempt to tackle the difficult task of evaluating differences in the behavior of "Leboyer babies" and their mothers contrasted with controls. Rather, it is another needed paper reporting the safety of many of the proposed modifications when experimental and control groups are compared. It seems desirable to lay to rest, through these and further studies, the misapprehension that these minimal changes, when applied to uncomplicated labors and births, can be harmful. When their safety has been established, well-planned and sensitive studies should then be able to show, over time, whether or not there is real benefit from incorporating them into obstetrical practices.

Even though data may be lacking, there is one essential point that should not be lost; that is, that changes in our care of the laboring mother, her partner, and their baby that lead to a greater sense of satisfaction from their childbirth experience, result in more effective parent-infant bonding. The Leboyer approach is safe, cost-effective, and feasible for many institutions and can not be resisted on any rational basis. Indeed, the time has come when we must examine our conduct in every pregnancy, regardless of the risk or outcome, to discover those human factors that we must appreciate and preserve in order to help every couple emerge from their childbirth experience with greater insight, knowledge, and competence.

JOHN W. GROVER, MD
Chairman
Division of Obstetrics and Gynecology
Lutheran General Hospital
Park Ridge, IL 60068

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The New York State Tumor Registry

An important resource

This issue of the *Journal* features a report by Polednak et al[1] on the epidemiology of bone cancers in upstate New York, based on data from the New York State Tumor Registry. Registries such as this one encompass all cases that occur in a defined population at risk, providing unbiased estimates of the frequency of various cancers among subgroups in the population. This approach has assisted in implicating causes of several cancers: diet and breast and colon cancer,[2] diethylstilbestrol and vaginal cancer,[3] and alcohol and cancer of the oral cavity.[4]

There have been few epidemiologic studies of bone cancer, however, because of its rarity (less than 2 in 100,000 per year in the United States). The current report, which is based on a population of 10.5 million, shows a pattern consistent with other studies[5] that have found a correspondence between the age of occurrence of bone growth in childhood and Paget's disease in adults.

Descriptive epidemiology is but one of the many tools used to narrow and identify the causes of cancer at any site. Others include laboratory, clinical, case-control, and cohort studies. The present study is an example of how hypotheses are generated in the investigative process.

The state registry was established in 1940, and since 1973 has included cancers diagnosed in New York City residents. This expansion provides important clues to the causes of cancer occurrence in city residents as well as more complete reporting for upstate residents who received care in the city.

The state registry has been used to confirm associations between risk factors and cancer, to pinpoint geographic areas with excessive cancer occurrence,[6] and to identify subgroups with high or low risks of cancer.[7] For example, a study of risk factors for breast cancer in Nassau County residents was based on registry data that showed an age-adjusted occurrence 15 percent higher than for other New York State residents.[8] In addition, the registry is assisting a study to determine why gastrointestinal cancers rarely occur in individuals from Puerto Rico.

The registry serves another purpose in allaying unnecessary concerns of residents about the risk of developing cancer.[9] Registry data from 1955 through 1977 showed no evidence for higher cancer rates associated with residence near the Love Canal toxic waste burial site, in comparison with the entire state outside of New York City. The data were all the more convincing because they were obtained on a routine basis from a standardized reporting system and before the widespread publicity, so that recall and selectivity biases were not likely. Because of unknown latency periods for most tumors and the small size of the study population there is the possibility for some excess risk at present or in the future. Nevertheless, the availability of registry data allowed a prompt and scientifically sound assessment of past and present risk.

These are but a few of the many uses of the New York State Tumor Registry which is, and will continue to be, a valuable state resource.

JOSEPH FELDMAN, DrPH
Associate Professor
Department of Preventive Medicine
and Community Health
State University of New York
Downstate Medical Center
New York, NY 11203

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AN APPRECIATION

Alfred A. Angrist, MD, 1902–1984

Alfred A. Angrist, MD died March 19, 1984 at the age of 81. In December 1982, Dr Angrist retired as Editor of the *Journal*, a position he had held with great distinction since 1972.

Born in Brooklyn, New York on March 25, 1902, Dr Angrist received his BS degree from the College of the City of New York in 1922 and his MD degree from the Long Island College of Medicine in 1926. In 1929 he was appointed instructor in pathology at the New York Medical College. Between 1934 and 1948, Dr Angrist was associate professor of pathology at New York Medical College. In 1935 he became pathologist and director of laboratories at the Queens Hospital Center, a position he held until 1954 when he became Professor and Chairman of the Department of Pathology of the Albert Einstein College of Medicine, Yeshiva University. At the same time, he became director of laboratory services at the Bronx Municipal Hospital Center.

In 1967, students and physicians at the Albert Einstein College of Medicine established the Alfred A. Angrist Alumni Association in his honor.

Dr Angrist contributed 279 papers to the medical literature, reflecting not only his research interests, but also the many difficult social and philosophical issues facing medicine.

Members of the Alfred A. Angrist Alumni Association, consisting of his former students and residents, contributed to a festschrift of Dr Angrist, published as the May 1983 issue of the Journal.

LETTERS TO THE EDITOR

Address correspondence to Editor, New York State Journal of Medicine, *420 Lakeville Road, Lake Success, NY 11042. Letters should be typed double-spaced and include the signature, academic degree, professional affiliation, and address of each author. Preference is given to letters not exceeding 450 words, and every effort will be made to assure prompt publication. All letters are personally acknowledged by the Editor.*

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After a man's heart...
when smokers find out the good things Chesterfields give them
Nothing else will do

The following letters were selected from more than 200 received in response to the December issue of the Journal. *Additional letters and manuscripts on "the world cigarette pandemic" will be published in future issues. The correspondence on this subject will* not *be closed.*

Pesticide residues in cigarettes

TO THE EDITOR: I have read with great interest the December 1983 issue of the *New York State Journal of Medicine.* I feel that you have missed an area concerning tobacco that may offer far more impact for efforts to curtail smoking than anything else.

In his discussion of tobacco-growing, Muller[1] alluded to the use of pesticides. In my experience, I have found that most people are unaware that tobacco is not considered a food crop by the Environmental Protection Agency or the United States Department of Agriculture. This is the result of heavy lobbying by the tobacco industry. The reason for the importance of this action is so that tobacco will not have the requirement of tolerance setting for pesticides that are used on the crop. All food crops that have pesticides used on them require exhaustive feeding studies in residue trials to determine the safe application levels under the labeling that is proposed. This applies to all pesticides of any type used on crops even though the pesticide may have been used one year previous to the planting of the crop. Tobacco, not being a food crop, is not tested for pesticide residues. The only "residue" work done is by the tobacco industry itself to determine if a candidate pesticide has any affect on the flavor testing program. This means that there is no control over pesticide residues in tobacco, including EDB, DDT, dieldrin, parathion, sevin, toxophene or a host of others. I find this fact appalling and often wonder why, with the environmental hammer so often used on pesticides, pesticide producers, and farmers, no one to my knowledge ever question the amount of pesticide residues in or on tobacco products.

JOHN E. PROCTOR
PO Box 4913
Hawthorn Road
Kansas City, MO 64120

The author works for a company that manufactures agricultural chemicals.

Editor's note: On March 3, the Associated Press reported from Hartford, Connecticut, that five tobacco growers, including Consolidated Cigar Corporation, were ordered by the state's Department of Environmental Protection to supply drinking water to 40 families

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[1] Muller M: Preventing tomorrow's epidemic. *NY State J Med* 1983; 83:1304.

whose wells were contaminated with the pesticide ethylene dibromide (EDB). For many years EDB was used routinely in 116 tobacco fields in the Connecticut River Valley, and tobacco is the only crop in the state on which EDB was used. The tobacco companies were also ordered to pay for a study of EDB contamination in the Connecticut River Valley and to monitor ground water near wells found to have EDB concentrations above the maximum allowable level.

Cigarettes and sports stars

TO THE EDITOR: In the excellent *New York State Journal of Medicine* of December 1983, devoted to smoking, I was impressed the most from a personal standpoint by the paper of Dr Mary Ann Cromer,[1] in which she pointed the finger at me along with Billie Jean King and Martina Navratilova for playing in professional tennis tournaments promoted by Virginia Slims cigarettes. In feeble defense I offer the following.

As professionals we had little choice but to play the "Slims" circuit because it was the major circuit of tournaments. To not play would be tantamount to stop earning a living from professional tennis. For Billie Jean and Martina this is not a realistic alternative. Fortunately for me, I have returned to the practice of medicine and I no longer play in professional events nor do I make any appearances at events sponsored by a cigarette manufacturer. I was never happy, nor am I now, with the fact that a cigarette company is the major promoter of women's professional tennis.

Just for the record let me add the following. Billie Jean King, Martina Navratilova, and Renée Richards are all three totally opposed to smoking and are dedicated to setting a healthy example for tennis players and non-tennis players alike.

RENÉE RICHARDS, MD
40 Park Avenue
New York, NY 10016

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[1] Cromer MA: "Precious baby." *NY State J Med* 1983; 83:1292.

In reply: Dr Richards and I seem to have very different points of view on alternatives to cigarette company sponsorship of sports and on the bargaining power of athletes over the products and settings to which their image is juxtaposed.

Although Martina Navratilova continues to participate in Philip Morris' Virginia Slims cigarettes tennis circuit and has worn an outfit at Wimbledon with the logo and colors of another cigarette brand, to the best of my knowledge neither she nor any other current professional tennis player has ever sported a non-smoking symbol on her uniform. Nor have there been any attempts to counteract the association of cigarette brands with the image of successful professional tennis players.

If women athletes—or the parents of participants as young as 14—truly wished to clear the air, they could demand that the tournament be renamed for something other than a cigarette brand name, that the cigarette advertising banners be removed from courtside and the scoreboards, that cigarette advertisements be deleted from souvenir programs, that free distribution of cigarettes be stopped, that the logo of the tournament be changed from that of a woman holding a tennis racket in one hand and a cigarette in the other, and that an alternate sponsor be sought.

Such changes would reduce the exploitation of women by the tobacco industry.

In a related incident, the Boston branch of the American Medical Women's Association has protested the use by a cigarette company of an athletic facility on the Boston University campus for the Virginia Slims tournament. But letters to the University's president have been largely ignored. Somehow I doubt an objection by Dr Richards would be similarly ignored. Would she care to prove me wrong?

MARY ANN CROMER, MD
Somerville Hospital
230 Highland Avenue
Somerville, MA 02143

The rare courage of public role models

TO THE EDITOR: Your December 1983 issue devoted entirely to smoking-related articles was a real landmark. You are to be commended for bringing together so many of the world's most authoritative voices, joined in outrage against smoking. As the head of Group Against Smoking Pollution (GASP) of Massachusetts for the last six years, I have learned firsthand how powerful the tobacco companies have made themselves, and how pervasively their network of influence extends around the world.

The proliferation of cigarette-sponsored sports and entertainment events, as referred to in the *Journal*, is particularly interesting since it reflects a strategy by which the industry enables its name and logo to become associated with socially redeeming cultural events. However, not all public figures have allowed their name and reputation to be exploited in this way.

For example, a world class runner and Boston Marathon winner, Bill Rodgers, refused to participate in a road race in New England last year after learning that one of the sponsors was a tobacco company (American Brands). This year in Canada, downhill ski champion Steve Podborski refused to accept the winner's cup in a major race in protest against the sponsorship by a tobacco company (R J Reynolds-MacDonald); the Canadian national slalom champion, Jim Read, returned his trophy for the same reason.

At the other end of the spectrum is Billie Jean King who when asked by GASP last year in Boston why she allows her name to be associated with Virginia Slims cigarettes, replied that she believes in "free enterprise and that it's up to the woman herself."

In the entertainment field, in 1982 GASP contacted several stars of a music series being promoted as the "Camel Concerts on the Common." Singers James Taylor and Peter, Paul, and Mary were outraged that they had not been told of the cigarette sponsorship and announced that they would perform in the concert series only if it were not associated with Camel cigarettes. In a cloud of unfavorable publicity, R J Reynolds pulled out.

These are instances where public figures have taken courageous stands against being involved in sophisticated and deceptive cigarette promotions. They provide models of action for all those athletes and entertainers who say it just can't be done.

RITA ADDISON
Group Against Smoking Pollution (GASP)
New England Deaconess Hospital
25 Deaconess Road
Boston, MA 02215

Defeating the tobacco lobby

TO THE EDITOR: On behalf of the American Heart Association I would like to commend the *New York State Journal of Medicine* for its excellent December edition devoted entirely to cigarette smoking.

While we have come a long way since the release of the first Surgeon General's Report on cigarette smoking and disease some 20 years ago we still have a long way to go. It will take hard work and concerted efforts if we are to truly fight the powerful tobacco industry.

Here in Washington, DC, the American Heart Association has joined with the American Cancer Society and the American Lung Association in the formation of a Coalition on Smoking OR Health. In addition to these three major voluntary organizations some 30 other major professional and voluntary organizations are working as an informal coalition to see that antismoking legislation is considered and enacted in the United States Congress. Last year we were successful in seeing the first rise in the federal cigarette excise tax in 30 years. This year we are concentrating on legislation known as the Comprehensive Smoking Prevention Education Acts (HR 3979 in the House and S 772 in the Senate). These bills would require that all cigarette packages and advertisements carry, in a new format, disease specific rotating warning labels. Two examples of the labels are:

Warning: Cigarette Smoking
- causes LUNG CANCER and EMPHYSEMA
- is a major cause of HEART DISEASE
- is ADDICTIVE and may result in DEATH

and,

Warning: Cigarette Smoking By Pregnant Women may result in
- MISCARRIAGE, PREMATURE BIRTHS, or
- LOW BIRTH WEIGHT

In addition to stronger warning labels, the legislation would also require the industry for the first time to disclose all chemical additives.

I would encourage every reader to write to his or her Representative and Senators. Only through constituent grass roots support can we take on the Tobacco Institute and its allies and win this one.

SCOTT BALLIN, JD
Legislative Counsel
American Heart Association
Office of Public Affairs
1110 Vermont Avenue NW, Suite 820
Washington, DC 20005

Hypocrisy on marijuana and tobacco

TO THE EDITOR: Your December 1983 issue on "The World Cigarette Pandemic" is a breath of fresh air in the polluted atmosphere of cigarette smoke. Your editorial should be distributed to every health professional in this country. It may move us from clouded discussions concerning the dangers of smoking to direct action.

There is one area that I feel should be stressed in any discussion on smoking. That is the issue of tobacco cigarette smoking and marijuana cigarette smoking. We spend millions of dollars in this country promoting tobacco smoking and millions of dollars controlling marijuana smoking.

I hope that a future issue will address this subject. It may help to channel some of the moral indignation in this country over marijuana smoking to moral indignation over tobacco smoking. These two major health issues belong together under addictive behavior and death.

MATT MARTIN
Chairperson
New Jersey Interagency Council on
Smoking and Health
129 E. Hanover Street, 4th floor
Trenton, NJ 08608

The author is Chief of Drug Treatment and Rehabilitation, Division of Narcotic and Drug Abuse Control, New Jersey State Department of Health.

Statewide physicians' lobby for clean indoor air

TO THE EDITOR: December's issue on smoking and health is to be applauded. In its scope, it touched most of the issues regarding smoking while never losing focus on medicine's misladen priority—preventive medicine and the war against smoking. There is a cigarette pandemic that physicians must address themselves to with greater verve, for only the medical community offers the vaccine to this rampant disease.

I know. Over the past year, I have been mustering efforts with others to facilitate passage of the New York Clean Indoor Air Act by attempting to activate physician support statewide. Previously, medical societies in New York have given verbal support, but this has not been backed up by individual action on the part of physicians. This token effort by the medical community has therefore had little impact on counteracting the tobacco industry and its well-financed lobbying efforts. The fourth largest lobby in the state, the tobacco industry has had its way in perpetuating the pandemic and maintaining its role as vector of death and disease, while the medical lobby, the third largest lobby in the state, seems to sit idly by.

An effort was undertaken to have resolutions passed at many hospitals across the state demonstrating percentages of physician support for the Clean Indoor Air Act. I relate one experience with such a resolution proposal at my home institution, Albany Medical Center Hospital, one of the state's leading medical facilities. Administrators said they could support the Clean Indoor Air Act in principle, but would not do so in writing because they deemed the proposal "political." A few other hospitals have argued the same. Such response saddens me, not only for my patients and their children, but for those not yet born. For what is at stake, political repercussions or people's health? And if we physicians will not be leaders and activists in issues of preventive medicine, then who will be?

BRUCE L. WOLF, MD
Medical Resident
Albany Medical Center
New Scotland Avenue
Albany, NY 12208

Origins of medical news

TO THE EDITOR: For too long we have permitted the media to manipulate medicine for its own interests. Obviously good health and medical news are good circulation builders, whether for the prestigious *New York Times* or the yellow scandal sheets. For too long the special advertising interests have prevented the presentation to the public of what they should know about cigarettes, smoking, and health.

There are other areas where medicine must assert itself. Alcohol is handled similarly by the press and television. The contrast that we as physicians see, of wards full of middle-aged and older patients suffering from cirrhosis, polyneuritides, and the mental anguish associated with alcohol, and the television image of "happy" young, attractive men and women gloriously guzzling beer, is a sad sight. Again, it sets the picture of an unfortunate role model for our young people.

The media are also quick to seize so-called medical breakthroughs. They do it, I am sure, with the aid of the publicity departments of our most prestigious pharmaceutical companies. The recent instance of the introduction of Oraflex, for example, in which the television and press barrage prior to its introduction encouraged my patients to request it from me even before I had an opportunity to digest the literature—in this case not even the manufacturer's handouts.

The authoritative journals have until now said nothing. The so-called "throw-away" journals are even less critical. One journal, which I shall leave nameless except that it shares with yours the term "New" and is regional to the northeastern United States, seems within the last few years to have joined the crowd. Often prior to the publication date and certainly before I receive my copy, there are blurbs on national television and in my local newspaper. Occasionally the message is good. But most often it is premature, of no immediate relevance, and trouble-making.

We need an honest voice for health in the marketplace. I am proud of our *Journal*.

LEONARD WOLIN, MD
Buffalo General Hospital
100 High Street
Buffalo, NY 14203

Congressional aid

TO THE EDITOR: "The World Cigarette Pandemic" is a fine compilation of the health issues facing all of us, smokers and non-smokers alike. I am pleased to report that we are making some headway here in Congress by taking steps to better educate the public about the hazards of cigarette smoking. Most recently, my colleague Congressman Waxman was successful in passing a bill out of his subcommittee requiring that stiff health-warning labels be printed on cigarettes.

I feel fortunate to have a California colleague leading the way on this issue. I'll certainly be supporting Mr Waxman in his ongoing efforts to curb the tobacco industry's influence in Congress.

DON EDWARDS
10th District, California
Congress of the United States
House of Representatives
Washington, DC 20515

Grand rounds topic

TO THE EDITOR: Congratulations on the December 1983 issue of the *Journal*. My spring grand rounds was already in the formative stages (on Cigarette Marketing—1984) when I saw your special issue. It not only is making my preparation easier, but it also has caught the interest of the department chairman at the hospital. As a result, each attendee at my rounds will receive a copy of the issue.

JOHN D. SLADE, MD
Rutgers Medical School
St. Peter's Medical Center
254 Easton Avenue
New Brunswick, NJ 08903

Newsroom view on smoking

TO THE EDITOR: Your December 1983 issue is an extraordinary effort—horrifying in what it so professionally reveals and so thoroughly documents, but wonderfully complete and readable! It will save those of us who hope to make changes in human health and the health care industry months of digging for support data.

KAREN WINEGAR
Feature Writer
Minneapolis *Star* and *Tribune*
425 Portland Avenue
Minneapolis, Minnesota 55488

Women and cigarettes: feminine Ms-stake

TO THE EDITOR: You deserve applause for your December issue on "The World Cigarette Pandemic." I found it extremely interesting, enlightening—and frightening to consider the power wielded by the tobacco companies.

The wife and secretary of an internist, I am distressed by the number of patients seriously ill from lung and heart disease who pass my desk reeking of cigarette smoke.

A feminist and member of Nassau (Long Island) National Organization for Women (NOW), I have long resented the industry's attempts to enlarge the women's market, particularly when, as in the case of Philip Morris' Virginia Slims, they try to sell us a hazardous substance through a perversion of feminist ideals. I hope you will allow us to use some of your material in our newsletter.

IRIS SIMON
850 Richmond Road
East Meadow, NY 11554

Tobacco companies; Good-ill ambassadors?

TO THE EDITOR: The December issue of the *Journal* is bound to become a powerful reference tool in the hands of private and government agencies trying to deal with an addiction which costs so much in illness, misery, and money all over the world. I am glad that you documented the bad effects that a few "ugly American" corporations are having on the health and economies of other parts of the world. However, I expect that the tobacco industry will continue to spend millions of dollars to tell people that the connection between cigarette smoking and lung cancer, among other things, is far from having been demonstrated. Everyone who works on this must either have a powerful capacity to deny facts, or else have no integrity.

The fact that this publication is by an organization as prestigious as the Medical Society of the State of New York only adds to its authority, but I think the publication in turn increases the prestige of the Society. You wrote that the issue was a year in the preparation, and I can imagine how much effort went into it on the part of many people. I think you are to be greatly congratulated on the product, which will bring us all many dividends in the time to come.

EDITH M. JURKA, MD
116 East 66th Street
New York, NY 10021

Reducing cigarette consumption at the county level

TO THE EDITOR: As President of the New York State Association of County Health Officials, I would like to commend the Medical Society of the State of New York for the strong and positive leadership they have shown in devoting an entire issue of the *New York State Journal of Medicine* to smoking-related health concerns.

County health directors across the state have long recognized the incredibly high levels of morbidity and mortality which could be prevented by even modest reductions in cigarette consumption within our respective communities, but have found it extremely difficult to take any more than limited action at the local level to deal with this issue.

Publication of the information provided in your December 1983 issue should be of substantial value in stimulating increased activities to counter smoking throughout New York State. Levels of morbidity and mortality are such that even modest success in reducing cigarette consumption can achieve significant health status improvement and health cost reductions.

JOEL L. NITZKIN, MD
President
New York State Association
of County Health Officials
c/o Monroe County Health Department
111 Westfall Road—Caller 632
Rochester, NY 14692

Hospital smoking policy: where there's a will . . .

TO THE EDITOR: The December issue was an excellent review of the subject of cigarette smoking. I only regret that publication in whole or in part may not extend into the mass media. Based upon many of the articles, such as Dr. Gitlitz' correspondence with *The New York Times*, one can see why this might not occur.

As a physician specializing in pulmonary disease, I have been interested in smoking and health since my earliest days in practice when I was involved in the care of many young patients with tuberculosis at Glenridge Hospital in Schenectady. I observed that patients who persisted in smoking had more severe symptoms and a slower rate of recovery than those who did not. Consequently, I began strongly advising these patients to discontinue their smoking.

When I became medical director and chief of staff in 1937 (and until my retirement in 1977), I prohibited smoking in both the hospital wards and the business offices. We did permit smoking in the staff lounge; sadly, it was the nurses both then and now who seemed to smoke the most. Overall, with few exceptions patients and personnel cooperated very well with the smoking ban. This made for a much better atmosphere for patients.

JAMES M. BLAKE, MD
150A Glenridge Road
Schenectady, NY 12302

Upbeat magazines

TO THE EDITOR: I very much appreciate the list of publications that do not accept cigarette advertising,[1] and I would like to add the names of three others that make excellent reading material for the office waiting room: *Alaska* (the monthly magazine of "life on the last frontier," $18); *The Alaska Journal* (a quarterly review of the art, literature and history of the North Country, $16); *Alaska Geographic* (official quarterly of the Alaska Geographic Society, included with annual membership of $30).

All three are available from Alaska Northwest Publishing Company, 130 Second Avenue South, Edmonds, WA 98020.

KATHY WELTZIN
Alaska Council on Prevention
of Alcohol and Drug Abuse
7521 Old Seward Highway
Anchorage, AK 99502

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1. Richards JW: A positive health strategy for the office waiting room. *NY State J Med* 1983; 83: 1358–1360.

The Journal *welcomes the names of other such publications.*

"You gotta die of something"

TO THE EDITOR: It is extremely encouraging to see an entire issue of a reputable medical journal devoted to the subject of cigarette smoking.

As a family physician practicing in a rural area, I have come to despise cigarette smoking and its effects on people's health. I could spend pages recounting stories of patients who have died prematurely as a result of their cigarette addiction. Sad to say, that I at least partially alienate several patients a week because I encourage them to stop smoking cigarettes immediately.

Thanks so much for putting together this December issue. I will certainly keep it in my permanent files.

DONALD F. BRAUTIGAM, MD
193 East Main Street
Westfield, NY 14787

The silence of *The Times*

TO THE EDITOR: George Gitlitz, MD is to be commended for his dedication and persistence in challenging *The New York Times* with respect to the serious issues involved in the *Times'* refusal to discuss publicly its policy of accepting widespread cigarette advertising.

Like so many social evils, tobacco smoking will never be cured so long as the financial rewards remain so great; in this instance, advertising revenues are the smoked glass by which the *Times* cannot see its way clear to apply its vaunted editorial principles.

JOSEPH J. MACDONALD, JD
MacDonald, Ryan & Jaekel
Counsellors at law
113 Prospect Street
Ridgewood, NJ 07451

Testimonial

TO THE EDITOR: The December 1983 issue of the *New York State Journal of Medicine* on the world cigarette pandemic is the best symposium on the subject that I have ever read. And as a repentant sinner I have read a great deal.

ABRAM J. ABELOFF, MD
130 East 77 St.
New York, NY 10021

Call for Translators

TO THE EDITOR: A Spanish edition, or abstract, if either is available, will be very much appreciated.

The highly important health problem of cigarette smoking, so well presented in this edition, prompts my request in behalf of our many non-English speaking Hispanics in this area.

M. F. WIENER, MD
3850 Galt Ocean Drive
Fort Lauderdale, FL 33308

No pussyfooting

TO THE EDITOR: Let me join the chorus who probably have already voiced their admiration for the splendid December 1983 issue of the *New York State Journal of Medicine*. It is a *tour de force*.

I have already ordered additional copies of that issue and plan to provide each of our county legislators with a copy. The Suffolk County Legislature is in the process of considering a Clean Indoor Air Act which would place restrictions on smoking in public places. Your issue on smoking and health should impel the men and women of the county legislature to take action.

DAVID HARRIS, MD, MPH
Commissioner
County of Suffolk
Department of Health Services
225 Rabro Drive East
Hauppauge, NY 11788

The measure passed, 13–5, on March 27.

For an ongoing campaign

TO THE EDITOR: I reviewed with interest the December 1983 issue of the *New York State Journal of Medicine*. I believe that devoting the entire issue to the subject of cigarette smoking was entirely appropriate. I urge the *Journal* to continue on this campaign and to do similar things in other areas (such as drunken driving) in the future.

JOHN H. MORTON, MD
Professor of Surgery
The University of
Rochester Medical Center
601 Elmwood Avenue
Rochester, NY 14642

Wider distribution urged

TO THE EDITOR: I wish to express my admiration for the comprehensive manner in which you researched the subject of smoking and the injuries it causes as reported by investigators worldwide.

Using the entire December 1983 issue of the *Journal* for that single subject must be a first in the annals of medical publications.

I would suggest that, since the articles are understandable by laymen, a copy should find its way to the desks of lawmakers throughout the world.

DAVID MEZZ, MD
3901 South Ocean Drive
Hollywood, FL 33019

STOP PRESS: President urges stepped up effort to counter smoking at the workplace

On March 13 the Health Insurance Association of America produced a video teleconference, "Wellness at the Worksite," viewed by corporate executives and representatives of the mass media in major cities across the country.

One of the featured speakers was President Ronald Reagan whose acknowledgment of the physical and economic toll taken by cigarette smoking was one of the strongest statements against smoking made by an American president in this century.

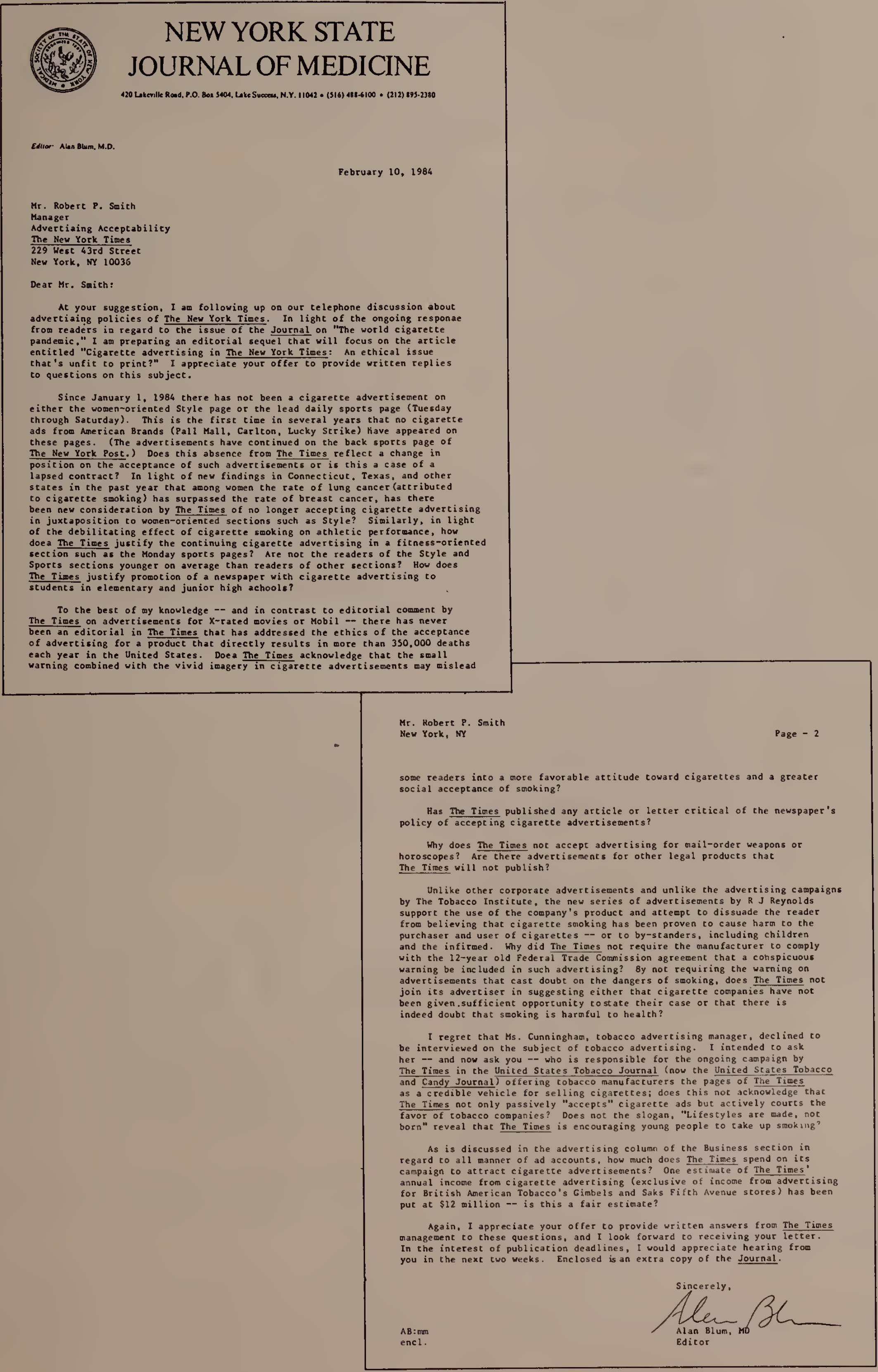
Yet few if any radio or television stations or newspapers reported on his comments.

Following is the text of his statement:

> I'd like to commend the insurance industry for the creativity, diligence, and foresight they've demonstrated in organizing this event. I appreciate being given an opportunity to contribute to your totally worthwhile endeavor.
>
> Disease prevention and health promotion is in all of our interests, not only for people in the insurance business, but for employees and employers throughout the wide spectrum of American enterprise. I don't need to tell you employers that the illness of your employees is a costly proposition. A healthier workforce means higher productivity, reduced absenteeism, and less overtime. In the long run, it also means a reduction in the cost for employee health benefits.
>
> Today we've conquered the old killers like smallpox, diphtheria, and polio. We understand that how each of us chooses to live will, more than anything else, determine our health.
>
> Executives are in a position to provide leadership in this area, because working people spend about half their waking hours at work. With little or no financial investment, the employer can influence his or her employees to change some bad habits that heavily affect one's health.
>
> Cigarette smoking is, perhaps, the best example. We all know how harmful it is. Well, the illness resulting from smoking is costly to both the smoker and his or her boss. A helping hand to assist employees to break the habit might be a wise investment.
>
> Good eating and exercise habits are another area employers could use their influence. We are all aware of the fitness programs in Japanese companies. It's something you might think about.
>
> I'm certain that this teleconference will provide enough ideas. The question now is whether you're willing to take the steps necessary to make a difference. Those of you who take this to heart have my sincere thanks.
>
> America can only be as strong and healthy as its people, and, as in all things, the only lasting change that takes place comes when each of us does his part to make our country the good and decent place we want it to be. Thanks for letting me do my part. God bless you.

Ethics of *The New York Times* under scrutiny

Many readers have expressed disbelief and anger over the failure of the publisher and editors of The Times *to address their own role in the promotion of disease and high medical costs through the publication of cigarette advertising. A promise by the manager of advertising acceptability for* The Times *to seek answers to a number of questions about the newspaper corporation's acquiescence in promotion of cigarette smoking led to the following letter.*



NEW YORK STATE
JOURNAL OF MEDICINE
420 Lakeville Road, P.O. Box 5404, Lake Success, N.Y. 11042 • (516) 488-6100 • (212) 895-2380

Editor Alan Blum, M.D.

February 10, 1984

Mr. Robert P. Smith
Manager
Advertiaing Acceptability
The New York Times
229 West 43rd Street
New York, NY 10036

Dear Mr. Smith:

At your suggestion, I am following up on our telephone discussion about advertiaing policies of The New York Times. In light of the ongoing responae from readers in regard to the issue of the Journal on "The world cigarette pandemic," I am preparing an editorial sequel that will focus on the article entitled "Cigarette advertising in The New York Times: An ethical issue that's unfit to print?" I appreciate your offer to provide written replies to questions on this subject.

Since January 1, 1984 there has not been a cigarette advertisement on either the women-oriented Style page or the lead daily sports page (Tuesday through Saturday). This is the first time in several years that no cigarette ads from American Brands (Pall Mall, Carlton, Lucky Strike) have appeared on these pages. (The advertisements have continued on the back sports page of The New York Post.) Does this absence from The Times reflect a change in position on the acceptance of such advertisements or is this a case of a lapsed contract? In light of new findings in Connecticut, Texas, and other states in the past year that among women the rate of lung cancer (attributed to cigarette smoking) has surpassed the rate of breast cancer, has there been new consideration by The Times of no longer accepting cigarette advertising in juxtaposition to women-oriented sections such as Style? Similarly, in light of the debilitating effect of cigarette smoking on athletic performance, how doea The Times justify the continuing cigarette advertising in a fitness-oriented section such as the Monday sports pages? Are not the readers of the Style and Sports sections younger on average than readers of other sections? How does The Times justify promotion of a newspaper with cigarette advertising to students in elementary and junior high achools?

To the best of my knowledge -- and in contrast to editorial comment by The Times on advertisements for X-rated movies or Mobil -- there has never been an editorial in The Times that has addressed the ethics of the acceptance of advertising for a product that directly results in more than 350,000 deaths each year in the United States. Doea The Times acknowledge that the small warning combined with the vivid imagery in cigarette advertisements may mislead

Mr. Robert P. Smith
New York, NY
Page - 2

some readers into a more favorable attitude toward cigarettes and a greater social acceptance of smoking?

Has The Times published any article or letter critical of the newspaper's policy of accepting cigarette advertisements?

Why does The Times not accept advertising for mail-order weapons or horoscopes? Are there advertisements for other legal products that The Times will not publish?

Unlike other corporate advertisements and unlike the advertising campaigns by The Tobacco Institute, the new series of advertisements by R J Reynolds support the use of the company's product and attempt to dissuade the reader from believing that cigarette smoking has been proven to cause harm to the purchaser and user of cigarettes -- or to by-standers, including children and the infirmed. Why did The Times not require the manufacturer to comply with the 12-year old Federal Trade Commission agreement that a conspicuous warning be included in such advertising? 8y not requiring the warning on advertisements that cast doubt on the dangers of smoking, does The Times not join its advertiser in suggesting either that cigarette companies have not been given sufficient opportunity to state their case or that there is indeed doubt that smoking is harmful to health?

I regret that Ms. Cunningham, tobacco advertising manager, declined to be interviewed on the subject of tobacco advertising. I intended to ask her -- and now ask you -- who is responsible for the ongoing campaign by The Times in the United States Tobacco Journal (now the United States Tobacco and Candy Journal) offering tobacco manufacturers the pages of The Times as a credible vehicle for selling cigarettes; does this not acknowledge that The Times not only passively "accepts" cigarette ads but actively courts the favor of tobacco companies? Does not the slogan, "Lifestyles are made, not born" reveal that The Times is encouraging young people to take up smoking?

As is discussed in the advertising column of the Business section in regard to all manner of ad accounts, how much does The Times spend on its campaign to attract cigarette advertisements? One estimate of The Times' annual income from cigarette advertising (exclusive of income from advertising for British American Tobacco's Gimbels and Saks Fifth Avenue stores) has been put at $12 million -- is this a fair estimate?

Again, I appreciate your offer to provide written answers from The Times management to these questions, and I look forward to receiving your letter. In the interest of publication deadlines, I would appreciate hearing from you in the next two weeks. Enclosed is an extra copy of the Journal.

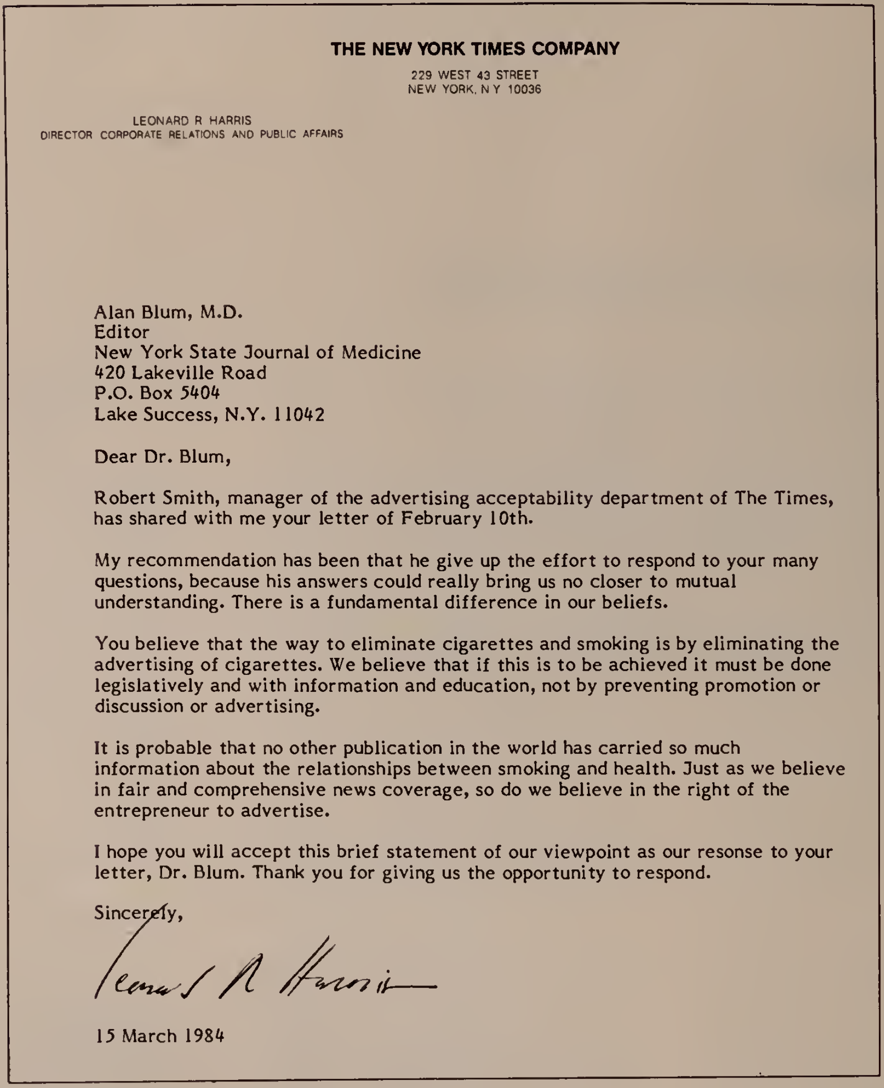
Sincerely,

Alan Blum

Alan Blum, MD
Editor

AB:mm
encl.

Reply from The New York Times Company



THE NEW YORK TIMES COMPANY
229 WEST 43 STREET
NEW YORK, N Y 10036

LEONARD R HARRIS
DIRECTOR CORPORATE RELATIONS AND PUBLIC AFFAIRS

Alan Blum, M.D.
Editor
New York State Journal of Medicine
420 Lakeville Road
P.O. Box 5404
Lake Success, N.Y. 11042

Dear Dr. Blum,

Robert Smith, manager of the advertising acceptability department of The Times, has shared with me your letter of February 10th.

My recommendation has been that he give up the effort to respond to your many questions, because his answers could really bring us no closer to mutual understanding. There is a fundamental difference in our beliefs.

You believe that the way to eliminate cigarettes and smoking is by eliminating the advertising of cigarettes. We believe that if this is to be achieved it must be done legislatively and with information and education, not by preventing promotion or discussion or advertising.

It is probable that no other publication in the world has carried so much information about the relationships between smoking and health. Just as we believe in fair and comprehensive news coverage, so do we believe in the right of the entrepreneur to advertise.

I hope you will accept this brief statement of our viewpoint as our resonse to your letter, Dr. Blum. Thank you for giving us the opportunity to respond.

Sincerely,

Leonard R Harris

15 March 1984

Changing maternal and newborn care

A study of the Leboyer approach to childbirth management

DAVID KLIOT, MD, LOUISE SILVERSTEIN, PHD

ABSTRACT The Leboyer approach to childbirth is defined and presented as a family-centered model. To evaluate the safety and physiologic efficacy of the Leboyer modifications as compared to conventional delivery procedures, three groups of infants were compared: a Leboyer early-clamped group, a Leboyer late-clamped group, and a control group. A range of physiologic parameters was assessed over the first 72 hours postpartum, including body temperature, residual mucus, heart rate patterns, blood pH, and bilirubin levels. No significant differences were found between groups in any of the physiologic measures. In all groups values were within the normal range for newborn physiologic functioning. These findings suggest that the Leboyer modifications examined in this study are safe for most healthy newborn infants and that many "routine" procedures, such as high intensity lighting, sterile draping, nasopharyngeal suctioning, and immediate separation of mother and infant, do not need to be maintained as standard obstetrical practice.

(NY State J Med 1984; 84:169–174)

INTRODUCTION

Family-centered maternity/newborn care can be defined as the delivery of safe, quality health care while recognizing, focusing on and adapting to both the physical and psychosocial needs of the client-patient, the family and the newly born. The emphasis is on the provision of maternity/newborn health care which fosters family unity while maintaining physical safety.[1]

Current trends in obstetric training and practice emphasize the importance of a family-centered, psychosocial orientation to childbirth; this is in contrast to the former emphasis on the technical management of labor and delivery. Frederick Leboyer[2] describes modifications in early newborn care that represent one alternative to traditional hospital procedures. Leboyer's interest is in decreasing the trauma of birth for the infant. However, his approach can be extended to provide a different experience for the entire family.

Although Leboyer's procedures contrast with accepted delivery room management, in only one controlled study to date, by Nelson,[3] have the physiologic effects of his approach been investigated. In the only systematic research study in which behavioral characteristics were examined (as measured by a neonatal neurobehavioral scale), Silverstein[4] found no differences between infants delivered in accordance with the Leboyer procedure and a control group. In the absence of a large body of direct research evidence, the medical profession has been reluctant to accept departures from standard practice that is known to be safe.

In this paper we will describe Leboyer management and report the findings of a clinical study in which the Leboyer approach is compared to standard obstetric procedures. Although the number of experimental subjects was limited and the control sample small, this study represents an initial examination of the controversial questions that have been raised concerning this orientation to childbirth. The results will also be discussed in the context of recent research data on neonatal adaptability and mother-infant attachment.

The Leboyer approach to childbirth. Leboyer, Gimbel and Nocon[5] have described his technique as follows: (1) Low ambient light and low noise levels are maintained in the delivery room. (2) The newborn is placed face-down in a flexed position on the mother's unprepped, undraped abdomen and gently massaged by the mother and obstetrician for a period of five to 10 minutes. (3) The umbilical cord is severed either when pulsations cease or after five to 10 minutes. (4) Nasopharyngeal suctioning is not performed. (5) The infant is not actively resuscitated or stimulated to initiate respiration. (6) The infant is bathed in warm water for five to 10 minutes.

Although Leboyer has delivered over 1,000 infants using these procedures, he has not investigated the results on infant physiology or behavior. Preliminary behavioral observations of children delivered by the Leboyer approach have been reported.

Rapoport[6] studied 120 children between the ages of one and three who had been delivered by Leboyer. This sample was not self-selected, since the patients had been assigned to Leboyer in a maternity clinic. Rapoport found that these youngsters scored within the normal range of a standardized IQ test (a French modification of the Gesell scale). This finding, however, is difficult to interpret since Rapoport did not include a control group of youngsters from the same population. Rapoport's most interesting finding is the absence of psychosomatic eating and sleeping disorders in 110 of the 120 children.

Salter[7] observed the state of six newborn infants delivered by standard obstetric procedures and six newborn infants delivered by the Leboyer approach. Although she did not

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From the Department of Obstetrics and Gynecology (Dr Kliot) and the Department of Psychiatry (Dr Silverstein), State University of New York, Downstate Medical Center, Brooklyn, New York.

Address correspondence to Dr Kliot, 225 Marlborough Road, Brooklyn, NY 11226.

subject her data to statistical analysis, she reported that the Leboyer infants spent more time in the quiet-alert state than control group babies during the 15 minute observation periods within the first 24 to 30 hours postpartum.

Oliver and Oliver[8] observed the spontaneous behavior of 17 Leboyer and 17 control group infants during the first 15 minutes after delivery. They found that the Leboyer infants spent significantly more time with eyes open and hand muscles relaxed than did control group infants.

These early studies of the Leboyer modifications suggest that this approach may decrease internal physiologic tension, increase alertness, and decrease the incidence of psychosomatic difficulties.

Research questions raised by the Leboyer management of early newborn care. In order to highlight the contrast between Leboyer and standard management techniques, conventional procedures (as summarized by Behrman[9]) are presented:

> Immediately after delivery, the baby should be restrained with the head slightly dependent, while the cord is clamped and cut. The infant should then be placed supine on a table, the head kept low with a slight lateral tilt. A nurse should listen to the heartbeat immediately . . . the physician should aspirate the mouth, pharynx and nose with a catheter . . . lightly slapping the soles frequently aids in initiating a deep breath and crying. To diminish evaporative heat loss, the baby should be dried at once. Further heat loss . . . should be prevented by . . . placing the baby in an incubator, enclosing him in a silver swaddler or plastic bag, or providing a microenvironment of radiant heat over the resuscitation table.

The degree of Leboyer's departure from standard practice and the absence of scientific evidence concerning the effects of his procedures have generated a number of controversial questions concerning the safety of his technique. These questions were the focal points for the design of the current study: (1) Is low ambient light adequate for managing the events of delivery and for assessing the neonate's physical status? (2) Without overt physical stimulation by the obstetrician, for example, slapping the heels, can the infant establish effective oxygenation? (3) Is postural drainage in a face-down position as effective as suctioning with a DeLee catheter in a supine position? (4) Does exposure to the potentially contaminating conditions of the mother's hands and undraped, unprepped abdomen lead to bacterial infection? (5) Does exposure to the air-cooled ambient temperature of a modern delivery room environment lead to cold stress? (6) Does placement of the infant above the level of the uterus and late cord clamping cause placental transfusion or exsanguination?

METHODS

Design. The study design included three groups of subjects. In order to isolate the effects of late cord clamping (the possibility of placental transfusion or exsanguination of the neonate) from the effects of the other Leboyer procedures, two groups of Leboyer babies were studied and compared to a control group of babies delivered by standard obstetric techniques. In addition, the safety of the Leboyer modifications was evaluated by comparing the physiologic data in the "Leboyer" groups to normal values of neonatal functioning.

In Leboyer Group 1, the cord was clamped within 60 seconds, whereas in Leboyer Group 2, cord clamping was delayed 10 minutes. The 10-minute interval was used to encompass all variations in timing of cessation of placental functioning. To limit the variables that might affect physiology in the newborn; Leboyer's procedure of bathing the neonate in warm water was not included in either Leboyer group. The following procedures were used in both Leboyer groups: (1) The delivery room was lit by a 100 watt light bulb reflected off the wall (When more light was necessary, for example, for episiotomy repair, or vaginal examination, spot lighting was used for perineal illumination so that the infant could remain in a dimly lit environment.). (2) The staff was encouraged to maintain a low noise level. (3) Immediately after birth, the infant was placed face down on the mother's undraped and unprepped abdomen. (4) The infant was gently massaged for five to 10 minutes by the mother and/or obstetrician. (5) Nasopharyngeal suctioning by bulk or DeLee type catheter was not carried out (In the presence of meconium-stained amniotic fluid, the infant was to be carefully monitored by the obstetrician and, if necessary, suctioned by an endotracheal catheter placed under direct visualization. A small number of infants did have minor meconium staining and were adequately managed without suctioning.). (6) No overt physical stimulation (for example, slapping feet) was applied by the obstetrician to initiate respiration or crying. (7) The infant was then dried and placed in a radiant warmer, treated with silver nitrate and vitamin K, and footprinted and banded. The following procedures were used for the control group: (1) Standard delivery room lighting was used. (2) No effort was made to limit the noise level. (3) The cord was clamped within 60 seconds after birth. (4) The infant was cradled in the physician's arms with its head in a dependent position while the cord was clamped and bulb suctioning performed. (5) The infant was then dried and placed in a radiant warmer, treated with silver nitrate and vitamin K, and footprinted and banded.

Subjects. At the time of registration for postnatal care, all subjects seen in a private obstetrics practice over a four-month period were invited to participate in the study. Each patient was given a consent form approved by the institutional review committee of the Brookdale Hospital Medical Center, which described Leboyer modifications and the assessment procedures (for example, electronic monitoring, blood sampling techniques) to be used in the study. Patients agreeing to Leboyer management were assigned at random to one of the Leboyer groups. Patients who were not willing to have Leboyer management, but who were willing to have their infants studied by the assessment procedures described in the consent form, were placed in the control group. Leboyer Groups 1 and 2 included 39 and 40 subjects, respectively. Twelve subjects consented to be in the control group.

Cesarian section deliveries were not included in the study because of the higher incidence of pathologic situations associated with this group of patients. However, since the purpose of the study was to observe the effects of the Leboyer modifications in the context of a wide range of normal obstetric conditions, subjects were not screened for parity, gestational age, presenting position or forceps delivery. In addition, a variety of standard analgesic and anesthetic techniques were used.

The social and medical characteristics of the sample population are presented in Table I. Two of the 91 mothers were black; the other mothers were white, middle to upper-middle class. The mothers ranged in age from 18 to 35 years. Most deliveries were spontaneous vaginal or forceps deliveries; either no anesthesia or a local anesthetic was used. The majority of infants had normal gestation periods (38 to 42 weeks), weighed between 2,500 and 4,000 g and had Apgar scores of 8 at one and five minutes. Thus the study sample represents a group of normal mothers and infants with uncomplicated and only slightly medicated deliveries.

Assessment procedures. There was concern that effective evaluation of the infant might be compromised in a dimly lit environment since the Apgar score, the traditional index used for assessing early newborn functioning, requires visual observation. Therefore, in this study it was elected to use heart rate patterns, in addition to the Apgar score, as the primary index for evaluat-

TABLE I. Social and Medical Characteristics of Mothers and Infants Participating in the Study

	Leboyer Group 1	Leboyer Group 2	Control Group
Mothers			
Mean age (yr)	26	25	24
Mean number of previous children	1	1	1
Infants			
Mean gestational age (wk)	39.9	39.9	39.5
Mean birth weight	7 lb 3 oz	7 lb 2 oz	7 lb
Obstetric procedures			
Anesthesia			
None	14	11	0
Local	7	20	2
Pudendal	5	1	0
Spinal	1	2	1
Epidural	12	6	8
General	0	0	1
Type of delivery			
Spontaneous	25	37	7
Induced	2	0	0
Breech	2	0	0
Low or mid forceps	10	3	5

ing newborn status at birth. Heart rate immediately after birth was obtained by either palpation or continuous monitoring using corometric fetal monitors. Heart rate obtained by observation was also recorded at the time of the infant's admission to the nursery and at 12 and 24 hours postpartum.

The effectiveness of postural drainage was assessed in the two Leboyer groups by suctioning of residual mucus (using a DeLee catheter at 10 minutes).

Temperature regulation was monitored by recordings of rectal temperature at 5, 10 and 15 minutes after birth. Temperature values were obtained by either a mercury thermometer or by a constantly-recording rectal probe.

Hematocrit, bilirubin, and pH blood values obtained by venipuncture were used to evaluate hypertransfusion, exsanguination, bilirubinemia, and metabolic status.

Length of hospital stay, complication at discharge, and readmissions were recorded to monitor neonatal morbidity and infection.

RESULTS

Two series of separate univariate analyses of variance were computed for each variable. In the first series all three groups were compared simultaneously, whereas in the second series only the Leboyer groups were compared. The results are presented in Table II. No significant differences between groups for any of the physiologic variables were found in either series of comparisons. In addition, observed values for all groups were found to be within the normal range of newborn physiologic functioning.

The typical heart rate pattern showed an initial decrease at birth, below the antepartum baseline level, followed by a postpartum increase of 10 to 20 beats per minute above the antepartum rate (Fig 1). Similar relations between antepartum and postpartum heart rate patterns have been described by James and Adamson,[10] and Goodlin and Horowitz,[11] but not used in clinical assessment. In our study, this early pattern of compensatory tachycardia observed in all babies was associated with normal physiologic findings.

In the current study, it was elected not to apply physical stimulation (other than gentle message) to induce breathing, and to use heart rate patterns rather than overt crying as the criterion for assessing effective oxygenation. The normal range of Apgar scores (Table II) indicates that the infants in the Leboyer groups were able to establish effective oxygenation and ventilation without physical stimulation. In most cases, respiration was established without crying.

A minimal amount of residual mucus (approximately 2 mL) was obtained from infants in the Leboyer groups at 10 minutes postpartum, indicating that postural drainage and back massage were effective in clearing the nasopharyngeal space.

In the present study, the normal range of the infants' temperatures at 24 hours indicates that exposure to the mothers' hands and abdominal skin did not increase the incidence of bacterial infection. In addition, none of the infants in the Leboyer groups exhibited symp-

TABLE II. Mean Physiologic Values for Leboyer and Control Group Infants

Physiologic Measures	Normal Range*	LeBoyer Late-Clamped Group $\bar{x}$	SD	(N)	LeBoyer Early-Clamped Group $\bar{x}$	SD	(N)	Control Group $\bar{x}$	SD	(N)
Rectal temperature (°C)	36.8–37.8									
5 minutes		37.5	0.86	(37)	37.6	0.83	(36)	37.5	0.76	(9)
10 minutes		37.3	0.92	(38)	37.4	0.98	(36)	37.3	0.69	(6)
15 minutes		36.9	1.1	(33)	37.0	0.94	(30)	36.9	0.71	(5)
24 hours		36.7	1.0	(21)	37.2	1.12	(16)	37.0	1.48	(4)
Heart rate (beats/min)	120–160									
Immediate		154.1	11.0	(19)	151.5	9.0	(16)	153.6	13.2	(8)
12 hours		139.5	15.9	(31)	141.4	11.2	(33)	141.2	7.7	(5)
24 hours		133.9	12.1	(20)	137.4	9.7	(26)	130.1	17.8	(8)
Hematocrit (%)	44–61									
12 hours		59.8	6.8	(24)	58.6	5.6	(22)	59.8	9.5	(5)
24 hours		60.9	5.4	(9)	55.7	8.2	(12)	59.4	5.3	(3)
Bilirubin (mg/100 ml)										
12 hours	<5	3.27	3.3	(29)	2.5	1.7	(28)	2.2	0.8	(8)
24 hours	<12	5.5	3.9	(30)	5.7	2.7	(29)	4.7	2.3	(8)
Blood pH	>7.25									
12 hours		7.3	0.08	(25)	7.3	0.07	(34)	7.3	0.09	(6)
24 hours		7.3	0.07	(11)	7.4	0.08	(16)	7.4	0.07	(3)
Apgar score	8–10									
1 minute		9.0	0.5	(39)	8.9	0.9	(40)	9.0	0.4	(12)
5 minutes		9.9	0.3	(39)	9.9	0.5	(40)	9.8	0.4	(12)

* Values from Smith and Nelson, 1976.[9]

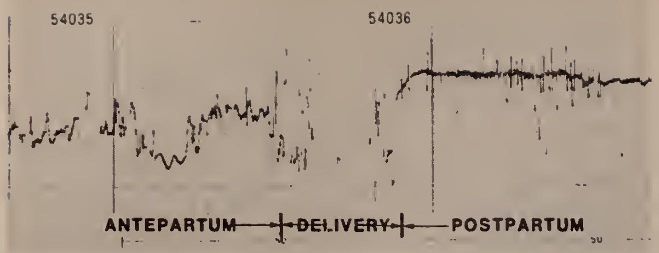

FIGURE 1. Typical heart rate pattern.

toms of cold stress or evidence of excessive heat loss. This suggests that the mother's body was an effective heat source in maintaining adequate body temperature.

Although the hematocrit values of infants in all three groups in the current study were at the high end of the normal range, the combination of late cord clamping and placement of the infant above the level of the uterus did not cause either hypertransfusion or exsanguination. In addition, the lack of in-hospital treatment of jaundice and the absence of extended hospital stays or readmissions indicate that the Leboyer approach did not increase susceptibility to jaundice for this sample of infants.

DISCUSSION

This study cannot be considered a definitive examination of the effects of the Leboyer approach because of the design limitations discussed earlier. However, the absence of significant differences among all three groups and the equivalence of values in the Leboyer groups to normal physiologic values indicate that, for the infants involved in this study, the Leboyer modifications were safe. The results further suggest that such "routine" procedures as high intensity lighting, sterile draping of the mother's abdomen, nasopharyngeal suctioning, and immediate separation of mother and infant may not need to be maintained as standard obstetric practice.

In terms of the six research questions presented earlier, the findings suggest the following tentative conclusions.

Delivery room evaluation. In the current study, low ambient light was adequate for delivering the infant, even when forceps manipulation was necessary. Monitoring heart rate patterns proved to be an acceptable method for evaluating newborn status at birth and was feasible in the dimly lit environment of a Leboyer delivery.

Establishment of effective ventilation and oxygenation. Although the mechanisms involved in the onset of respiration are not yet well understood, standard management of the newborn continues to stress supplementary physical stimulation. Yet the majority of healthy newborns have been shown to breathe spontaneously and to establish effective respiration without specific physical stimulation. In the current study, newborns were able to establish effective oxygenation and ventilation with gentle massage rather than more vigorous physical stimulation.

Mucus drainage. Early management of the newborn is concerned with aspiration of the nasopharyngeal mucus above the level of the trachea. The conventional procedure is to hold the neonate in either a head-dependent position or a supine position and to remove the mucus by bulb suctioning or DeLee catheter. Figure 2 illustrates that placement of the neonate in a supine position may actually increase mucus aspiration, whereas placement in a face down position enhances drainage through the mouth and nose, thereby decreasing the possibility of aspiration. The Leboyer procedure used in the present study combines postural drainage with back massage. This approach has the additional advantage of avoiding complications associated with more invasive techniques, such as those reported by Cordero and Hon.[13]

Perinatal infection. The immaturity of the neonatal immunologic system renders the neonate particularly susceptible to infection from "new" organisms. Standard procedures developed in response to this vulnerability have included restricting early mother-infant contact. Thus the mother's abdomen is covered with sterile drapes, and mother and infant are not allowed tactile contact until several hours after birth. In the present study, exposure to the mother's hands and abdominal skin did not increase the incidence of infection.

Temperature stress. A modern delivery room environment is approximately 10°C below the infant's neutral environment temperature of 32°C to 34°C.[14] Continued exposure of the newborn to this cool ambient environment has been shown to cause a cold stress syndrome including metabolic acidosis, relative hypoxemia, hypoglycemia, and increased renal water loss.[15,16] Conventional hospital procedures deal with these problems through the use of prewarmed incubators or radiant warmers. Phillips,[17] departing from standard management, reported that infants who had been dried and covered could be held by their mothers on the delivery table for 15 minutes without having hypothermia.

Similarly, the Leboyer approach places the infant in a flexed position, skin-to-skin with the mother's abdomen and exposed to the ambient environmental temperature. The results of the present study indicate that the mother's body is also an effective heat source in maintaining adequate body temperature.

Early versus late cord clamping. Differences have been reported in the circulatory, respiratory and renal function of early and late-clamped infants.[18,19] The implications of these differences for early extrauterine adjustment have been the subject of persistent controversy. Yao and Lind[20]

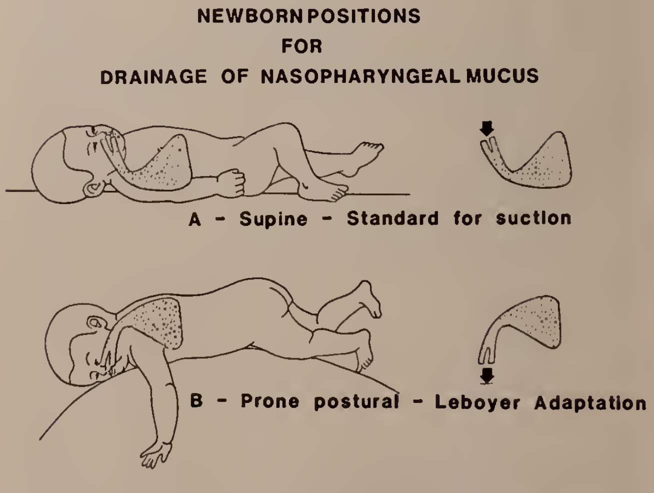
NEWBORN POSITIONS
FOR
DRAINAGE OF NASOPHARYNGEAL MUCUS
A - Supine - Standard for suction
B - Prone postural - Leboyer Adaptation

FIGURE 2. Positions for newborns to drain nasopharyngeal mucus.

concluded that the neonate's adaptive capacities are stressed by the placental transfusion usually associated with late clamping, whereas Dunn[21] and Redmond[22] proposed that placental transfusion can have beneficial effects; for example, it can delay the onset of the asphyxia that triggers respiration at birth, increase iron stores, and contribute to fluid balance over the first few postpartum days.

Within the context of the Leboyer approach, the controversy is further complicated since the infant is placed on the mother's abdomen before the cord is clamped. Yao and Lind[23] reported that placing the newborn 50 to 60 cm above the level of the introitus for three minutes before cord clamping lessened or prevented placental transfusion. The current findings indicate that for this sample, late cord clamping did not increase susceptibility to jaundice.

Thus, in the current study an attempt was made to provide a basis for changing the procedural management of early newborn care and the atmosphere of the delivery room. The results of this study illustrate that when changes are instituted in the context of current scientific information and using modern techniques of monitoring newborn status, stringent management is not necessary for the safety of healthy infants.

Standard delivery room procedures evolved based on a concern for minimizing infant morbidity and mortality and in the context of an outdated understanding of the newborn infant as a passive and undifferentiated organism.[24] Recent research has shown the neonate to be an active, stimulus-seeking organism sensitive to even subtle environmental manipulations.[25,26] This new understanding of neonatal competence and sensitivity has generated a concern for the dramatic adaptational adjustments required of the infant at birth. A corresponding awareness has emerged concerning the psychologic stress that parturition places on the mother to develop an immediate positive attachment to her newborn infant.[27]

These adaptational requirements of mothers and infants have now become major considerations in the management of labor and delivery. Hospital procedures that may hinder newborn adaptation, such as use of the supine position during labor, use of obstetric medication, and routine circumcision, are now being questioned.[28,29] Similarly, current literature on child development emphasizes the importance of maximizing opportunities for early wakeful parent-infant interaction.[30-33]

These recent findings have generated consumer demands for minimizing medical intervention and increasing patient participation.[34,35] The Leboyer procedures represent an approach to childbirth management that is responsive both to the concerns for limiting the adaptational stress to mother and infant and to consumer demands for more active participation. This approach has the advantages of minimizing the invasive techniques to which the infant is subjected and providing a transitional period of early parent-infant contact. This technique suggests an alternative method of patient-staff interaction in which the experience of childbirth in an institutional setting can meet the psychological as well as medical needs of the entire family.

We believe that further study of the relationship between the fetal and newborn heart rate patterns at the time of birth may be useful in assessing the newborn. The compensatory tachycardia after birth that has been associated with normal physiology may be an early indicator of postpartum newborn distress if the postpartum rate remains at the prebirth level or below.

Since completion of this study, I have delivered more than 1,500 infants incorporating the Leboyer bath into the management technique. (Fathers have been actively included in the childbirth experience by allowing them to give the infant the bath.) A modified Leboyer procedure using postural drainage and the bath have been utilized with Cesarian section births. No detrimental effects to the neonates have been observed.—DK

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Descriptive epidemiology of primary bone cancers in upstate New York

ANTHONY P. POLEDNAK, PHD, NANCY J. ELLISH, DRPH, PHILIP C. NASCA, PHD

ABSTRACT **Analyses of descriptive epidemiologic data from the population-based New York State Cancer Registry on 426 histologically confirmed cases of bone cancer diagnosed between 1974 and 1979 have supported previous findings on incidence rates according to age, sex, histology, and anatomic site. Some of these patterns may be explained by the association of bone cancer risk with rates of bone growth in childhood and with the occurrence of Paget's disease in adults. Differences in epidemiologic features among the histologic types analyzed (osteosarcoma, Ewing's sarcoma, and chondrosarcoma) suggest heterogeneity in causation.**

(NY State J Med 1984; 84:174-177)

INTRODUCTION

Bone cancer is a rare disease. Between 1973 and 1977 the average annual age-adjusted incidence rates per 100,000 people in the United States were 1.0 for males and 0.6 for females.[1] Comparable rates for residents in upstate New York (ie, New York State exclusive of New York City) between 1974 and 1979, based on data from the New York State Cancer Registry, were nearly identical to those in the United States—1.1 per 100,000 for males and 0.6 per 100,000 for females. Although these overall rates are low, a substantial proportion of cancers in children occur at this site, and rates also increase markedly in older age groups. Survival rates for most histologic types are poor, although there may have been some improvement for osteosarcoma since 1972.[2] Descriptive and analytical epidemiologic studies of bone cancers have been few, in part due to the small number of cases available for study.

We report here some descriptive epidemiologic characteristics of 426 cases of bone cancer among residents of upstate New York between 1974 and 1979 that were reported to the New York State Cancer Registry as histologically confirmed. Such descriptive studies may provide clues to etiology or evidence of etiologic heterogeneity among different subgroups of bone cancers. These data, derived from a population-based cancer registry, should be valuable in planning for treatment facilities and should increase awareness among physicians of associations (eg, age and sex differences, anatomic site patterns) and precursor conditions.

METHODS

The reporting of all cancer cases to the population-based New York State Cancer Registry has been legally mandated for upstate New York since 1940. Because of recent improvements in the registry, however, the years 1974 to 1979 were selected for detailed analysis. Since 1973, the data on cases identified in the registry by death certificate only (DCO) have been reviewed to obtain additional sociodemographic, clinical and histologic information. Beginning in 1973 cases diagnosed in New York City have been added to the registry. This has led to more complete reporting of cancers among upstate residents, especially those living in counties adjacent to New York City. On the basis of special studies in which cases identified in hospital records have been compared with those reported to the registry, reporting to the registry is estimated to be about 90 to 95 percent complete for upstate New York.

In this report we describe some characteristics of all cases of primary bone cancer (site 170, Ninth Revision of ICD) diagnosed among residents of upstate New York between 1974 and 1979 and reported to the New York State Cancer Registry. The year of diagnosis was used as the index date, and population data from the 1980 census were used for calculating incidence rates of bone cancer in the upstate New York population. The histologic type is coded according to the American Cancer Society's *Manual of Tumor Nomenclature and Coding.*[3] Because of the coding system used, certain cancers included under bone cancer in other studies[4] are not included here, for example, fibrosarcoma of bone and synovial sarcoma (coded to cancers of connective tissue, ICD 171), and lymphoma or reticulum cell sarcoma of bone (coded to lymphoma, ICD 200-202). Of the 495 cases reported as primary bone cancers (ICD site 170), 426 or 86.1 percent were confirmed by histologic tests. Because the majority of cases not confirmed were reported by DCO and undoubtedly included secondary bone cancers, these were excluded from analysis. As noted by Fraumeni and Boice,[4] the exclusion of these cases decreased incidence rates in older age groups, although the general patterns were not affected.

From the Cancer Control Section, Bureau of Chronic Disease Prevention, Division of Community Health and Epidemiology, New York State Department of Health, Albany, New York.

Address correspondence to Dr Polednak, Director, Special Studies Section, Bureau of Chronic Disease Prevention, Division of Community Health and Epidemiology, New York State Department of Health, Albany, NY 12237.

RESULTS

Age and sex distribution of patients with all types of bone cancers. Figure 1 shows the average annual age-specific incidence rates of bone cancers for all anatomic sites and histologic types combined. For both male and female subjects there is a bimodal distribution, representing cases in children and adults. For male subjects the incidence rate peaks at ages 15 to 19 and again at ages 65 to 69 and over 75. For female subjects, one peak occurs at ages 10 to 14 and the second peak at ages 65 to 69. The incidence rates are higher for males than for females, with the exception of those aged 30 to 34 and 70 to 74.

It should be noted that some rates are based on small numbers of bone cancers and are, therefore, subject to considerable statistical uncertainty. A measure of the reliability of each incidence rate is the standard error (SE) that can be estimated by dividing the rate by the square root of the number of cases upon which it is based.[1] For example, the incidence rate of bone cancer among males aged 15 to 19 years is 1.53 (Fig 1), based on 48 cases; the SE is 0.22, and the 95% confidence interval is 1.10 to 1.96 per 100,000.

The incidence of bone cancer varied from year to year. For male subjects, 39 cases were reported in 1974, 54 in 1975, 53 in 1976, 47 in 1977, 32 in 1978, and 50 in 1979. For female subjects, however, numbers were somewhat more constant—30 cases in 1974, 27 in 1975, 28 in 1976, 37 in 1977, 28 in 1978, and 31 in 1979. Crude annual incidence rates can be determined by using total populations from the 1980 census—5,064,284 males and 5,422,149 females in upstate New York)—and assuming a constant population over the period 1974 to 1979. Data on annual rates in broad age groups by sex also are available.

Anatomic site of all bone cancers by patients' age and sex. Figure 2 shows the age-specific incidence rates of bone cancer for all three predominant groups of anatomic sites. In general, incidence rates tend to be higher for males in almost all age groups. Childhood peaks occur about five years earlier in females than males for all three groups of sites.

Incidence rates are highest for the long bones of the lower limb, especially during childhood. These rates peak at ages 10 to 14 in females and 15 to 19 in males and increase again at older ages. For the pelvic bones, sacrum and coccyx, rates also peak at ages 10 to 19 and increase again at older ages. Cancers of the long bones of the upper limb and scapula show a somewhat similar pattern; childhood peaks are evident in both sexes.

Histologic type by age. On a proportional basis (Table I), 91% of histologically confirmed bone cancers in our series of adolescents (<20 years) are classified as osteosarcoma or Ewing's sarcoma, with the latter slightly more common. In adults (≥20 years) the major histologic types are osteosarcoma (35.9%) and chondrosarcoma (36.7%). Osteosarcoma, chondrosarcoma and Ewing's sarcoma together account for 85.7% of all bone cancers in this study. It should be recalled that fibrosarcomas and lymphomas of bone were not included.

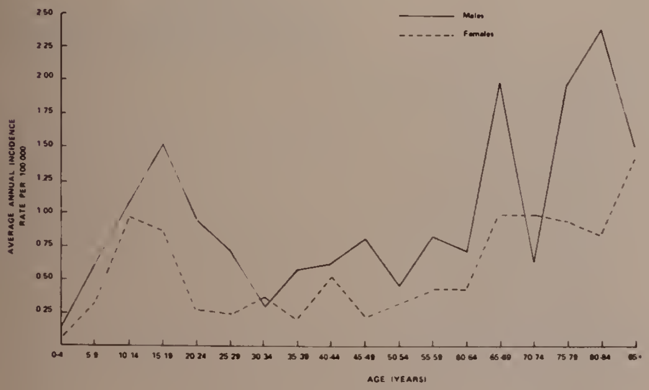

FIGURE 1. Average annual incidence rates per 100,000 for all primary bone cancers diagnosed among residents of upstate New York in 1974 to 1979, by age and sex.

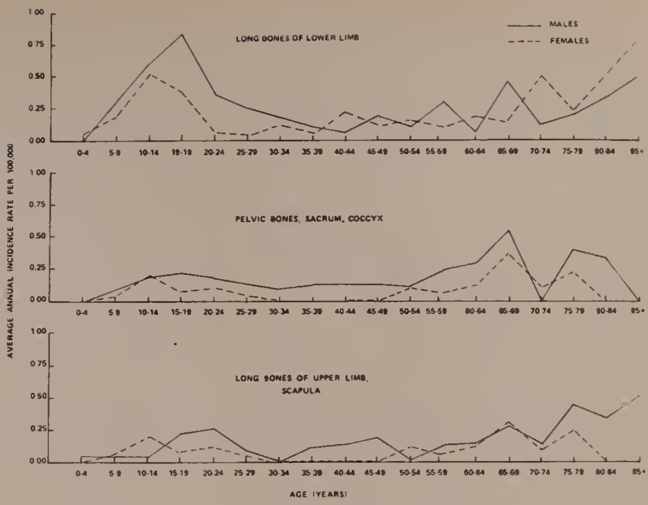

FIGURE 2. Average annual incidence rates per 100,000 for all primary bone cancers diagnosed among residents of upstate New York in 1974 to 1979, by anatomic site group, age and sex.

Chondrosarcoma, giant cell cancer and chordoma are proportionately more common, and Ewing's sarcoma much less common, in the adult versus adolescent groups with bone cancer.

Some of these apparent differences in age patterns by histologic type were further clarified by calculating age- and sex-specific incidence rates for the three major histologic types of bone cancer for males and females (Fig 3). Rates for Ewing's sarcoma peak at ages 10 to 19 years and then decline sharply; in almost all cases the diagnosis is made before age 35. In contrast, incidence rates for chondrosarcoma tend to increase steadily with age; in only a few cases is the diagnosis made before ages 15 to 19. Only osteosarcoma shows a distinct bimodal distribution, with rates peaking at 10 to 19 years of age and increasing again from about age 50 on. During childhood, an earlier peak in female versus male subjects is evident for osteosarcoma but not for Ewing's sarcoma or chondrosarcoma.

The number of bone cancers among nonwhite subjects was too small for detailed analysis by age and sex. It is noteworthy, however, that of the 13 cases in black patients none was Ewing's sarcoma and 10 were osteosarcoma, whereas the ratio of Ewing's sarcoma to osteosarcoma among white patients was 92 to 143.

The number of other histologic types (ie, chordomas and malignant giant cell tumors) was too small for calculating incidence rates. It is noteworthy, however, that the sex ratio (males to females) was 14 to 3 for chordomas versus 12 to 16 for giant cell cancers.

Anatomic site by histologic type. The number of cases within each histologic category is too small to calculate rates by anatomic site. Table II, however, shows some conspicuous differences in the distribution of anatomic sites among the histologic types and between cases in adolescents and adults. In adolescents the leg is the most common site for both osteosarcoma and Ewing's sarcoma, but the latter occurs at other sites (rib cage, vertebrae and pelvis) more frequently than osteosarcoma. In adults, as compared to children, osteosarcomas occur more frequently in the pelvis (19.6% versus 3.0%, $p < .005$) and less frequently in the leg (35.1% versus 71.2%, $p < .001$). Among adults, a larger proportion of chondrosarcomas than osteosarcomas occur in the rib cage (21.2% versus 2.1%, $p < .001$) and in the bones of the hand and wrist (6.1% versus 0.0%). On the basis of a small sample population, the most common site for the occurrence of Ewing's sarcoma in adolescents is the leg and in adults, the pelvis.

DISCUSSION

The bimodal age pattern for all histologically confirmed bone cancers (Fig 1) is largely due to osteosarcoma. As in other studies,[4] only osteosarcoma exhibits a bimodal age-incidence distribution, with two peaks of approximately

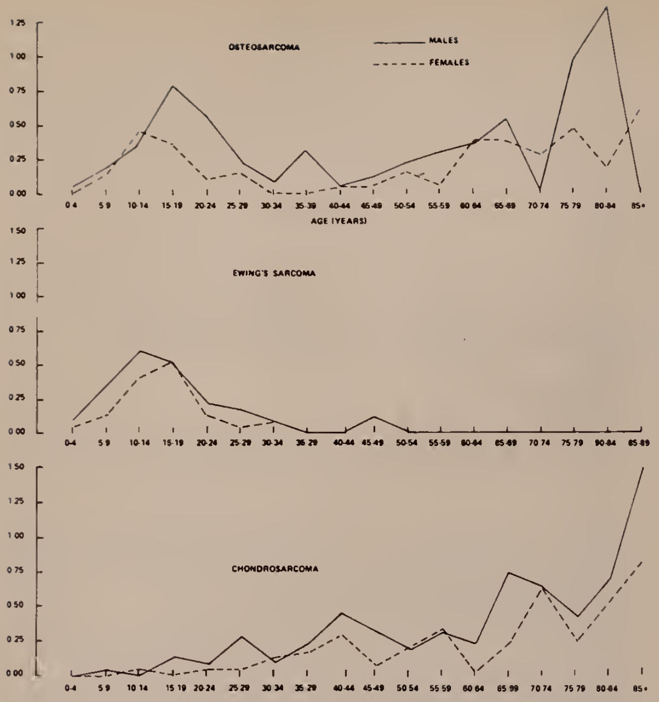

FIGURE 3. Average annual incidence rates per 100,000 for primary bone cancers diagnosed among residents of upstate New York in 1974 to 1979, by histologic type, age and sex.

equal magnitude (Fig 3). The increased incidence of chondrosarcoma at older ages (Fig 3) contributes to the high peak in total bone cancer incidence at older ages (Fig 1). The childhood peak for all bone cancers is due to Ewing's sarcoma and osteosarcoma, and especially to osteosarcoma of the long bones of the lower limb (Table II). Bone cancer incidence rates were low before the age of five years (Fig 1), with only four cases reported between 1974 and 1979 (three of Ewing's sarcoma and one of osteosarcoma). Similar findings were reported from the Third National Cancer Survey[4] and from the Mayo Clinic series.[5,6] Age-specific incidence rates for all bone cancers are consistently higher in males than females, with the exception of a few age categories for which rates are based on small sample populations.

There are at least two explanations for the patterns of distribution of bone cancers by sex, age and anatomic site. The first involves differential growth rates, and the second Paget's disease (osteitis deformans) which shows a predilection for certain bones as well as a distinct age and sex pattern. The earlier peak in osteosarcoma rates in girls (at ages 10 to 14) and a higher, later peak in boys (ages 15 to 19) (Fig 3), coupled with known patterns of human growth, led to the hypothesis of an association between bone cancer risk and periods of rapid growth.[7,8] The predominance in childhood of bone cancers in the knee region (Fig 2) may be related to greater growth activity at the distal versus the proximal femur.

The relationship between Paget's disease and bone cancers in adults was recognized by Paget in 1877. The high male to female ratio for Paget's disease at all sites and the increasing prevalence with age, especially after about 50 years, are noteworthy in view of the age and sex pattern of bone cancer in adults (Fig 1). Sarcomas complicating Paget's disease occur most frequently in the long bones, pelvis, and skull.[9] Although the proportion of bone cancers associated with Paget's disease in adults is uncertain and may be lower in the United States than in some European countries,[9] the increases in rates for bone cancers of the lower limb, pelvis, and long bones of the upper limb after about age 50 are noteworthy (Fig 2).

Osteosarcoma and Ewing's sarcoma differ in their histologic origin and in their distribution by age, sex and anatomic site (Fig 3, Table II). The peaks of both osteosarcoma and Ewing's sarcoma in adolescents suggest a relationship to skeletal growth, and Fraumeni[10] reported a tendency for children with both osteosarcoma and Ewing's sarcoma to be taller than controls (who had nonosseous cancer). Alternatively, the apparent absence of an earlier childhood peak in incidence rates for Ewing's sarcoma in females versus males, in contrast with osteosarcoma (Fig 3), suggests that factors other than accelerated growth may be involved in the causation of Ewing's sarcoma. Miller[11] has reviewed other contrasting epidemiologic features of Ewing's sarcoma and osteosarcoma in domestic animals and man. The rarity of Ewing's sarcoma among black subjects versus white subjects has been confirmed by several studies[11] and also appears to hold for the present series. The distribution by anatomic site appears to differ in children with Ewing's sarcoma versus those with osteosarcoma, with higher proportions of Ewing's sarcoma in the pelvis and rib cage (Table II).

Incidence rates for chondrosarcoma are low in childhood and increase with age, especially at ages 65 to 69 and older, and are consistently higher in men than in women (Fig 3). Similar findings were reported from the Third National Cancer Survey[4] and from Sweden.[12] The higher proportion of chondrosarcoma versus osteosarcoma occurring in the rib cage and hand and wrist in adults (Table II) is a further distinction in the descriptive epidemiology of these histologic types.[13] The costal cartilages undergo histologic changes with aging,[14] and such changes could conceivably affect the risk of chondrosarcoma.

TABLE I. Description of Primary Bone Cancer[a] Cases Diagnosed in Upstate New York Residents, 1974 to 1979

	Patient's Age at Diagnosis					
	<20 Years		≥20 Years		Total	
	No.	%[b]	No.	%	No.	%
Histologically confirmed (ACS code)[c]						
Osteosarcoma (918)	66	42.3	97	35.9	163	38.3
Chondrosarcoma (922)	6	3.8	99	36.7	105	24.6
Chondroblastoma (923)	2	1.3	1	0.4	3	0.7
Giant cell (925)	4	2.6	24	8.9	28	6.6
Ewing's sarcoma (926)	76	48.7	21	7.8	97	22.8
Ameloblastic sarcoma (931)	0	0.0	2	0.7	2	0.5
Chordoma (936)	0	0.0	17	6.3	17	4.0
Unspecified (800, 801)	2	1.3	9	3.3	11	2.6
Total histologically confirmed	156	100.0	270	100.0	426	100.0

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[a] ICDA code 170 (see text), histologically confirmed.

[b] Percent of cases among those reported as histologically confirmed.

[c] Excludes "sarcoma, not otherwise specified" (three cases) and a few cases of benign tumor types reported to the Cancer Registry.

TABLE II. Number and Percent of Bone Cancer Cases by Anatomic Site and Major Histologic Type, Upstate New York (1974 to 1979)

	<20 Years at Diagnosis				≥20 Years at Diagnosis					
	Osteosarcoma		Ewing's Sarcoma		Osteosarcoma		Chondrosarcoma		Ewing's Carcoma	
Anatomic Site	No.	%	No.	%	No.	%	No.	%	No.	%
170.0 Skull, face	2	3.0	1	1.3	6	6.2	2	2.0	0	0.0
170.1 Mandible	1	1.5	1	1.3	3	3.1	1	1.0	1	4.8
170.2 Vertebrae	—	—	4	5.3	3	3.1	3	3.0	2	9.5
170.3 Rib, sternum, clavicle	1	1.5	9	11.8	2	2.1	21	21.2	1	4.8
170.4 Arm, scapula	10	15.2	10	13.2	19	19.6	16	16.2	4	19.0
170.5 Hand, wrist	—	—	—	—	—	—	6	6.1	0	0.0
170.6 Pelvis	2	3.0	13	17.1	19	19.6	14	14.1	7	33.3
170.7 Leg	47	71.2	33	43.4	34	35.1	33	33.3	4	19.0
170.8 Foot, ankle	1	1.5	2	2.6	—	—	2	2.0	0	0.0
170.9 Unspecified	2	3.0	3	3.9	11	11.3	1	1.0	2	9.5
Total	66	100.0	76	100.0	97	100.0	99	100.0	21	100.0

The number of other histologic types of bone cancers (Table I) was too small for detailed analysis. All patients with chordoma were over 20 years of age (Table I), and the majority were males; similar trends have been reported.[6,13] The greater occurrence of giant cell cancers in adults versus adolescents (Table I) and the higher proportion of females to males (in contrast with most other histologic types of bone cancers) also have been reported in case series not derived from population-based registries.[6,15]

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Vascular access for patients on long-term hemodialysis maintenance

GEUN-EUN KIM, MD, HAGOP HOVAGUIMIAN, MD, ROBERT MATALON, MD

ABSTRACT One hundred and forty-nine vascular access procedures performed in 50 patients were reviewed. Radial artery cephalic vein side-to-side fistula (RA-CVS) was the procedure of choice with 96% immediate patency and 78% 12-month patency. An 84% immediate patency and a 41% 12-month patency were obtained in radial artery antecubital vein graft interposition fistula (RA-ACVG), and 88% immediate with 36% 12-month patency was obtained in brachial artery axillary vein graft interposition fistulas (BA-AXVG). Mean patency was 21.3 months with RA-CVS, 10.3 months with RA-AVC, 6.6 months with BA-AXV and 7.8 months with various salvage procedures. The patency rate of various salvage procedures in the thrombosed fistulas was equal to or better than new graft interposition and carried the advantages of a much shorter hospital stay and the ability for immediate use.

(NY State J Med 1984; 84:178–180)

INTRODUCTION

Internal arteriovenous (A-V) **fistulas,** created by surgical operation, have become the primary means of providing vascular access for long-term hemodialysis. Although long-term patency of the internal A-V fistula is superior to the external shunt, multiple operations to maintain patency are often necessary in the majority of patients.

We reviewed 149 vascular access procedures performed on 50 patients undergoing hemodialysis at our institution. We found that, with proper selection of the primary procedure and follow-up with well-planned revisions, such patients may not have to face the disastrous outcome that results from exhaustion of vascular access sites.

METHODS

Fifty patients who required vascular access procedures for long-term dialysis were studied from 1968 to 1981. All graft patency problems were evaluated by one nephrologist and one vascular surgeon who performed all 149 procedures. All procedures were carried out at the same institution, and there was a 95% follow-up. Primary procedures included 34 radial artery cephalic vein side-to-side fistulas (RA-CVS, Fig 1), as reported by Brescia et al,[1] 33 radial artery antecubital vein grafts interposition (RA-ACVG, Fig 1) and 17 brachial artery axillary vein grafts interposition (BA-AXVG, Fig 1). There were 61 "salvage" procedures consisting of two endarterectomies of inflow, three endarterectomies of outflow, five resections of hypertrophied vein valves, nine patch angioplasties, 29 dilations of stenotic areas using Bake's dilator, six vein swing procedures, three retrograde flow procedures (Fig 2) and four segmental interpositions (Fig 3).

Patients ranged in age from 29 to 93 years; the mean age was 58.4 years. Twenty patients with patent fistulas died during the follow-up period. Eleven patients were diabetic, and 29 were or had been hypertensive at one time. Forty bovine grafts, eight gortex (PTFE) grafts, and two saphenous vein grafts were used. All procedures were performed under local anesthesia with 3.5× magnification. RA-CVS procedures were performed whenever feasible. When the forearm veins were small, they were dilated with a No. 3 Fogarty embolectomy catheter before anastamosis; 7-0 or 8-0 Tevdek or prolene sutures were used, and frequently the lengths of venotomy and arteriotomy were 0.8 to 1.0 cm.

RA-ACVG and BA-AXVG procedures were performed as primary procedures when construction of standard RA-CVS fistulas was not feasible. Most often, this occurred when forearm veins were absent, or when a non-salvageable forearm A-V fistula was present.

Salvage procedures were performed after careful questioning of patients and staff with regard to problems during the dialysis before occlusion and after palpation of the fistula and observing for signs of tenderness. Incisions were made over or near the probable area of stenosis, and further evaluation was then made by careful sounding or introduction of a Fogarty catheter.

RESULTS

Patency of the fistula was calculated by the life table method. Immediate patency was 96% for RA-CVS, 84% for RA-ACVG, and 88% for BA-AXVG. Patency at 12 months was 78% for RA-CVS, a 2-fold greater patency rate than the latter two procedures (Table I, Fig 4). The longest patency of 132 months (11 years) was observed in a patient with RA-CVS. The longest patency for RA-ACVG was 27 months, for BA-AXVG 15 months, and for a salvage procedure 45 months. Mean patency interval as of December 1981 for RA-CVS was 21.3 months, for RA-ACVG 10.3 months, for BA-AXVG 6 months, and for salvage procedures 7.8 months (Table II).

Fogarty embolectomy catheters were used for dilation of the stenotic area in the early part of the study, but proved less effective than dilation with Bake's dilator, used during the latter part of the study period.

No patients died during or as a result of the procedure; there was a 1.3% immediate morbidity (2/149). A hematoma was evacuated and graft patency preserved in one of these two patients, and in the other patient an infection of the hematoma developed which required removal of the graft in one month. Long-term complications included six graft infections and six aneurysms.

Recognized causes of occlusions were 11 stenoses of inflow, 32 stenoses of outflow (of which five were due to hypertrophied vein valves) and four stenoses within the graft. Some patients were found to have multiple sites of stenosis.

The usual length of hospital stay for primary procedures was 10 days when the patient required immediate hemodialysis through the femoral route. Salvage procedures, when successful, resulted in an average hospital stay of two days; frequently, the patient was discharged within 24 hours. Only one disabling episode of hand ischemia was observed. This was in a patient who had undergone a side-to-side brachial artery basilic vein anastamosis for retrograde flow as a salvage procedure. The ischemia was corrected by ligation of the proximal basilic vein above the anastamosis (Fig 2). Blood transfusion was not necessary in any case. Disabling hand edema was observed in three patients with the RA-CVS procedure. This was corrected by ligation

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From the New York Infirmary-Beekman Downtown Hospital, New York City.
Address correspondence to Dr Kim, Director of Vascular Surgery, Department of Surgery, New York Infirmary-Beekman Downtown Hospital, 170 William Street, New York, NY 10038.

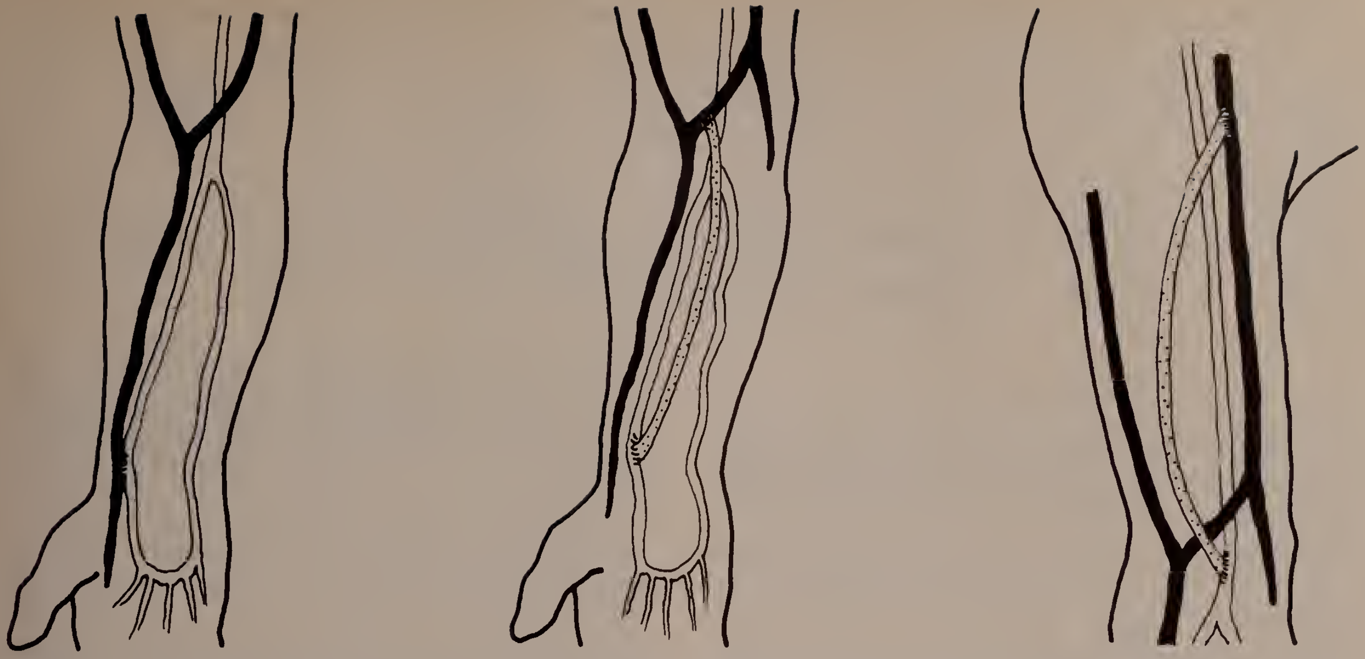

FIGURE 1. Left, radial artery cephalic vein side-to-side fistula (RA-CVS); Middle, radial artery antecubital vein graft interposition fistula (RA-ACVG); Right, brachial artery axillary vein graft interposition fistula (BA-AXVG).

of the distal feeding vein. No difference in patency was noted with regard to age, sex, or the presence or absence of diabetes or hypertension.

DISCUSSION

We have found that the ideal vascular access for long-term hemodialysis is the forearm radiocephalic A-V fistula described by Brescia.[1] Its patency proved to be the longest of all procedures, and options for salvage of the thrombosed RA-CVS fistulas are multiple and satisfactory in most cases. Long-term failures were often due to intimal hyperplasia, frequently noted at the outflow tract or at the anastamosis site or vein valve as reported by Baumann et al.[2] Mechanical dilation using a graded diameter Bake's dilator successfully reversed many stenoses caused by intimal hyperplasia in our patients, and long-term results have been satisfactory. This is consistent with results in the arterial system shown by Dotter and Gruntzig.[3,4] Other options include reversed fistula from the brachial artery to already dilated veins, vein swing of an adjacent large vein,

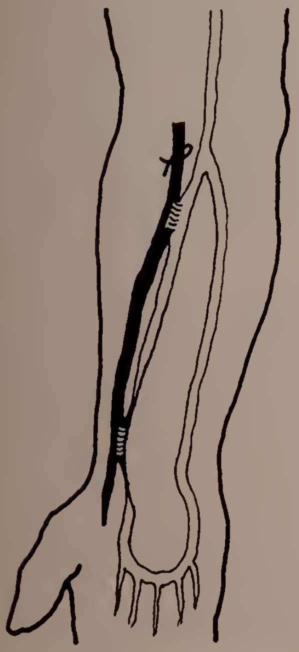

FIGURE 2. Brachial artery cephalic vein retrograde fistula.

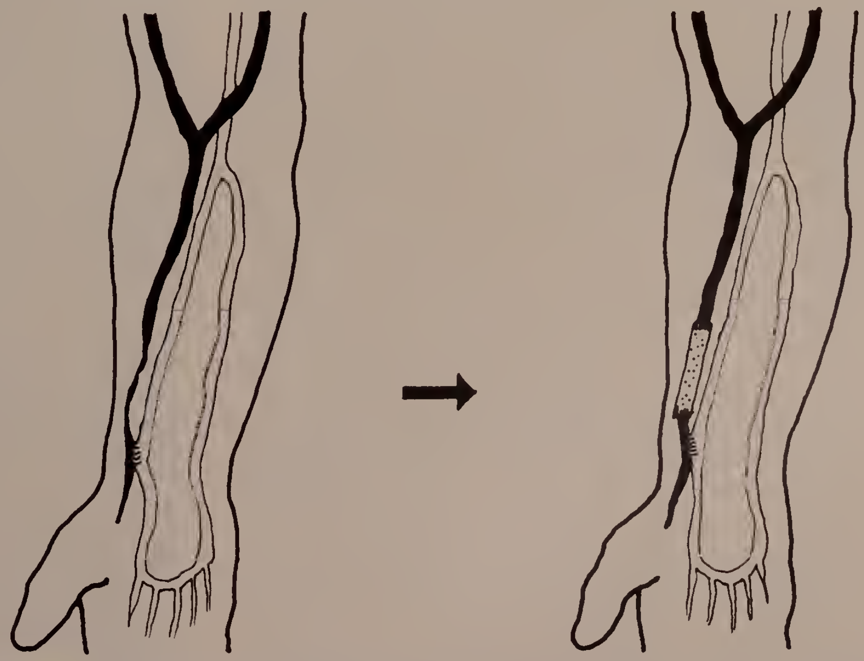

FIGURE 3. Left, stenosis or occlusion of arterio-venous fistula near the inflow; Right, segmental interposition of grafts.

TABLE I. Cumulative Patency of the Arteriovenous Fistulas

Patency	RA-CVS (%)	RA-ACVG (%)	BA-AXVG (%)
Immediate	96	84	88
Six months	81	57	54
12 months	78	41	36
18 months	57	16	—
24 months	57	16	—
30 months	45	—	—
36 months	45	—	—

TABLE II. Mean Patency Interval of the Arteriovenous Fistulas

Procedure	Mean Patency (months)
RA-CVS	21.3
RA-ACVG	10.3
BA-AXVG	6.6
Salvage	7.8

and interposition of short segments with vein or prosthesis. A dilated adjacent vein was found to be good graft material. The salvaged A-V fistulas were usually usuable immediately.

Hand edema is one of the less serious complications of the RA-CVS and is easily corrected by ligation and division of the distal feeding vein.

Although high cardiac output failure was reported by Ahern,[5] it was not observed in our patients even though some had two functioning fistulas or anastamoses greater than 1 cm in diameter.

Ischemia of the hand is rare and was observed in only two of our patients. Hand ischemia may be due to embolic phenomena either during or immediately after the procedure rather than a steal phenomenon since reversed flow from the ulnar artery was noted in RA-CVS by Anderson[6] and does not cause hand ischemia.

On many occasions, construction of the RA-CVS is not feasible because of inadequate forearm veins, caused by multiple venipunctures or by a venous cut-down procedure performed some time before consultation by the renal team. In these instances, RA-ACVG or BA-AXVG were performed. These procedures, although performed more quickly, carried a shorter life span and had a greater complication rate; they were therefore relegated to secondary procedures.

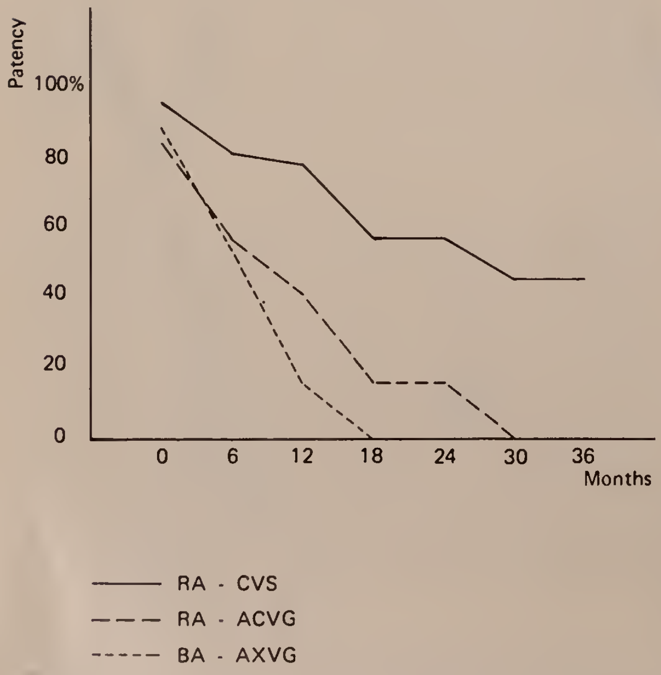

FIGURE 4. Patency (%) of the arteriovenous fistulas over a 36-month period.

Six infections required surgical treatment, with all occurring in the graft interposition. The incidence of infection was not different with bovine versus gortex (PTFE) grafts, but our series is too small to show any significant differences. Generally, infections occurred in patients with poor hygiene and in the drug addict population who often used their fistulas for intravenous drug administration.

Long-term patency of the bovine graft was not different from PTFE (gortex grafts). We have found bovine graft material is easier to handle for anastamosis to a small artery; however, early thrombectomy is more readily performed in gortex grafts. Routine use of angiography is advocated by Anderson,[7] but was used only in selected cases in this series.

Almost all salvage procedures were performed within 12 to 24 hours of detection of thrombosis. This may be a key factor both for successful surgical outcome and for detecting the cause of a failure. We have learned that the performance of vascular access procedures for hemodialysis is not a task to be delegated to the junior resident. The dialysis access procedure requires thorough knowledge of all the principles and techniques of vascular surgery with small vessels, more so in salvage procedures than in the creation of new fistulas. We have also found that with the participation of a readily available vascular surgeon experienced in the various techniques of A-V fistula surgery, the use of artery-to-artery and lower extremity fistulas was rarely necessary, and vascular access for hemodialysis could be maintained for many years.

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Lower extremity weakness, amenorrhea and galactorrhea in a 38-year-old woman

CASE PRESENTATION

Sergio Schwartzman, MD (Resident, Medicine): A 38-year-old woman was admitted to Queens Hospital Center complaining of bilateral lower extremity weakness, numbness, and pain for the preceding seven months.

The patient had been in good health until about eight months prior to admission, when amenorrhea and galactorrhea developed. She had had her last child seven years prior to admission; she had used birth control pills but denied any other medication. One month after the onset of galactorrhea, she noted weakness and paresthesia in both legs. At another hospital, she was told that she had phlebitis and was advised to discontinue use of the birth control pills. During that hospitalization, a CT scan of the head was performed and was reported to be within normal limits. The results of additional diagnostic evaluation studies at that time were not available to us.

Over the next five months the patient became progressively weaker. One month prior to the Queens Hospital admission, at a second hospital, a CT scan of the head showed questionable thinning of the clinoid processes. An endocrine work-up revealed a serum T4 of 1.3 μg (normal 4 to 12 μg), a thyroid-stimulating hormone (TSH) level of 1.9 microunits (normal 0.5 to 3.5 mU), a follicle-stimulating hormone (FSH) level of 2 milli-International Units (normal 4 to 30 mIU), and a prolactin level of 50 ng/mL (normal 2 to 15 ng); the AM cortisol level was 18.5 μg/100 mL (normal 5 to 25 μg).

The patient was told that she had hypothyroidism, was given thyroid medication and discharged.

Approximately one week later, she injured her right ankle, ambulation became increasingly more difficult, and she was finally bed-ridden due to profound weakness in her legs. About this time, the patient noted the onset of occasional episodes of urinary incontinence. On admission to Queens Hospital Center, she complained of weakness and paresthesia in both of her legs, inability to walk, urinary incontinence, chills and fever. She denied back pain, history of disc disease, fecal incontinence, headaches, head trauma, seizures, hot-cold intolerance, constipation or hyperdefecation, goiter, polyphagia, polydipsia, polyuria, change in weight, change in hand or foot size, visual disturbances, arthritis, rash, adenopathy, or conjunctival irritation. She was not taking any medications.

She denied the use of alcohol, drugs, or tobacco. Review of systems, past medical history, and family medical history were not contributory.

On admission, the physical examination revealed an obese black woman sitting comfortably in bed. Her blood pressure was 110/70 mm Hg; the heart rate was 120 and respiratory rate 18/min; her temperature was 101°F. Her skin was dry and warm, without rashes, petechiae, or ecchymoses. Her sclerae were white and conjunctivae pink; funduscopic examination showed only temporal pallor of the right optic disc. The thyroid was not enlarged. No lymphadenopathy was palpable in any location. There was a milky discharge from both nipples. Her lungs were clear; there was a grade I/VI systolic ejection murmur at the left lower sternal border. The abdomen was obese and not otherwise notable. Pelvic examination revealed a foul-smelling yellowish discharge but was otherwise within normal limits. Rectal examination disclosed no abnormalities; stool Guaiac test result was negative. Straight-leg raising produced pain in both calves, without tenderness on local palpation. The findings on general examination were otherwise negative.

The neurologic examination indicated full orientation; strength was decreased uniformly in the legs in both proximal and distal muscle groups. The deep tendon reflexes were decreased at the ankles and knees and were normal in the arms. Plantars were flexor, without clonus. The remainder of the neurologic examination was within normal limits.

The patient's complete blood count, blood indices, platelet count, percent of reticulocytes, and sedimentation rate were normal. The differential white blood count showed 6 percent eosinophils. The serum electrolyte, urea, nitrogen, and creatinine levels were normal; the serum glucose was 237 mg/dL. The serum glutamic oxalic transaminase (SGOT) was 84 units/mL (normal 10 to 40 units), and the lactic dehydrogenase (LDH) 275 units/mL (normal 60 to 120 units); the alkaline phosphatase was 97 IU/L (normal 13 to 39 IU). Serum bilirubin, total serum protein, albumin/globulin ratio, serum cholesterol, serum calcium, and serum inorganic phosphorus levels were normal. The serum uric acid was 10.4 mg/dL (normal 3 to 7 mg) and the creatine phosphokinase (CPK) level was 153 mU/mL (normal 5 to 35 mU).

The urine was acid and showed only one plus glucose on

Based on the clinicopathologic conference (CPC) held at the Long Island Jewish-Hillside Medical Center, New Hyde Park, New York, August 5, 1983.

Moderator: Marc Yunis, MD, Department of Medicine.

Clinical Discussion: Harry Steinberg, MD, Chief, Pulmonary Medicine.

Pathology Presentation: Laura Molho, MD, Assistant clinical professor of pathology, State University of New York at Stony Brook.

Editor: JOHN T. FLYNN, MD

Address correspondence to Dr Flynn, Consulting Editor, *New York State Journal of Medicine*, PO Box 5404, 420 Lakeville Rd, Lake Success, NY 11042.

dipstick.

The arterial blood gas determinations showed a pH of 7.47, a $P\mathrm{CO}_2$ of 32 and a $P\mathrm{O}_2$ of 91 mm Hg.

The chest film and abdominal flat-plate were both within normal limits. The electrocardiogram showed no abnormalities other than a sinus tachycardia of 110/min.

The vaginal smear was positive for *Trichomonas vaginalis*, and the patient was treated with metronidazole. Subsequent blood glucose determinations were all within normal limits. Blood cultures on the day of admission were positive for *Staphylococcus* and the patient was treated with oxacillin. She became afebrile, but one week later again became febrile; urine culture showed gram-negative rods sensitive to cefoxitin, which was added in therapy, and she again became afebrile. Antibiotic treatment was discontinued on the 21st hospital day, without further temperature elevations.

Subsequently, during the patient's two-month hospital stay, extensive endocrinologic evaluation was completed (Table I). The serum osmolality was 289 mosm/kg of water (normal 285 to 295 mosm); the urine osmolality was not determined.

An extensive neurologic work-up included three spinal taps, one of which was made prior to a myelogram. The CSF pressure on all determinations was normal; the fluid was always clear. The cerebrospinal fluid glucose was uniformly decreased on three occasions, 34 mg, 30 mg, and 28 mg/dL. The CSF protein level was elevated at 168 and 101 mg/dL (normal 15 to 45 mg) on two occasions; other protein determinations were not available. The CSF chloride was normal; the WBC count was 23 and 22/cu ml (normal 0 to 5 mononuclear cells) on two occasions, with 19 monocytes and 4 polymorphonuclear leukocytes. The RBC count in the CSF was 1 and 8/cu ml. The findings on electrophoretic studies for monoclonal protein bands, routine bacterial cultures, cultures for acid-fast bacteria and fungi, India-ink preparations and antigen determinations for cryptococcosis, and cytologic studies were all negative. The myelogram was within normal limits. Spinal films showed only sclerosis of the right sacroiliac joint. The skull film was reported to show questionable thickening at the base of the skull. CT scan of the head was interpreted as equivocal, with a questionable lesion of the pituitary stalk. Formal visual fields were notable for a superior-nasal field defect on the right. Electromyograms were consistent with a polyneuropathy of the lower extremities.

Immunologic studies included determinations of antinuclear antibody, rheumatoid factor, and VDRL; the results of all were negative. Two PPD skin tests for tuberculosis were negative (250 TU strength). Testing on two occasions with an anergy panel was negative; serum immunoglobulin studies revealed normal levels of IgG, IgA and IgM.

Bone marrow aspirate and biopsy disclosed no abnormalities. Mammography and liver-spleen scan were negative. Bone scan showed increased uptake at the right sacroiliac joint, but was otherwise within normal limits. Gallium scan showed increased uptake in the lungs.

During prolonged hospitalization, the patient became progressively weaker, with strength in the lower extremities reduced to 0 to 5. She became completely incontinent of urine. A diagnostic procedure was performed.

Harry Steinberg, MD (Chief, Pulmonary Medicine, LIJ-HMC, Assistant Professor of Medicine, SUNY at Stony Brook): This black female patient, 38 years old, presented with amenorrhea, galactorrhea, and profound weakness of the lower extremities. She also had increased susceptibility to infection. All of her laboratory data demonstrate pituitary dysfunction, with depression of all the anterior pituitary hormones except prolactin. The gallium scan of the lung showed abnormalities.

In contrast to other anterior pituitary hormones, the neuroendocrine control of prolactin is predominately inhibitory.[1] Lesions of the hypothalamus that interrupt the integrity of the hypothalamic-pituitary axis can result in depression of all the anterior pituitary hormones, with an actual reduction in the inhibitory effect upon prolactin release and consequently a rise in serum prolactin levels.

Many entities can cause an increase in serum prolactin.[2–4] The possibility of a prolactin-producing tumor must be considered in this case. This lesion occurs most commonly in women, and approximately 50 percent of these patients present with galactorrhea and abnormalities of menstrual function. Prolactinemia probably interferes with luteinizing hormone-releasing factor, with resulting anovulation and hypoestrogenemia. The important point, however, is that plasma levels of prolactin are usually very high with prolactin-producing tumors, usually more than 200 ng/mL. In this patient, the level was below 100 ng but

TABLE I. Endocrine Evaluation by Provocative Testing

		TRH + Insulin-Induced Hypoglycemia				
Hormone	Normal Level	Baseline Before Test	½ hr	1 hr	1½ hr	2 hr
Cortisol	5-25 μg	1.6	5.3	4.5	4.8	4.6
T-3	0.3-2 μg	0.5	...	...	...	...
T-4	4-13 μg	2.4	...	...	...	...
TSH	0-7 mU	1.3	2.0	2.0	...	...
FSH	5-20 mIU	1.5	...	...	...	...
Prolactin	5-25 ng	67	103.6	94	...	...
LH	5-22 mU	2.5	...	...	...	...
Growth hormone	7 + ng	<1	...	...	<1	<1
Metapyrone test	No response					

it could still be compatible with a small prolactin-producing tumor.

Methods of diagnosing such a tumor involve use of the major inhibitory factor for prolactin, dopamine. Administration of dopaminergic types of drugs leads to stimulation of the inhibitory factor and depresses prolactin levels. The administration of l-dopa plus a dopa decarboxylase inhibitor will depress the serum prolactin level in most instances, except in the presence of prolactin-producing tumors. The H2 antagonist, cimetidine, has been found to depress prolactin in most situations, but not with prolactin-producing tumors. Any means of inhibiting the uptake of dopamine will result in an increase of dopa in the central nervous system and again inhibit most causes of hyperprolactinemia, except that caused by tumors.

To make an unequivocal diagnosis of prolactin-secreting tumor, neuroradiologic evidence of the presence of the tumor is required. Review of the skull films and the CT scan in this patient showed them to be completely within normal limits. Occasionally, very small tumors that produce prolactin will not show on x-ray film and consequently are difficult to diagnose.

Most pharmacologic agents that tend to produce prolactinemia inhibit dopamine. Any chemical that can inhibit monoamine synthesis such as alpha methyl dopa, or monoamine depleters such as reserpine, or dopamine receptor antagonists such as phenothiazines or haloperidol will tend to cause prolactinemia. Other drugs with as yet undefined mechanisms, such as cimetidine, can cause prolactinemia. In this case, there was no evidence of drug ingestion.

Other conditions that can result in prolactinemia include hypothyroidism, which can occasionally be associated with galactorrhea. This patient was hypothyroid, but, as we shall see, the spinal fluid changes are impossible to explain on that basis. Renal failure can cause an increased synthesis of prolactin and a decrease in its clearance, but it would not apply to this patient. Hepatic cirrhosis can be associated with false neurotransmitters that lead to hyperprolactinemia, but again it does not apply here.

Ectopic production of prolactin is a rare complication of lung neoplasm and of renal adenocarcinoma. In this case, we would have to assume the presence of an occult lung carcinoma, one that was not visible on x-ray film, or a renal carcinoma; either neoplasm would have had to produce metastatic carcinomatous meningitis with its attendant spinal fluid changes. In such instances, we should expect a positive spinal fluid cytologic study.

Chest wall disorders that involve stimulation of the fourth to the sixth thoracic nerves can result in galactorrhea and hyperprolactinemia, but again this concept does not seem pertinent to this case.

There are many idiopathic causes of hyperprolactinemia, such as in the post-partum period or following withdrawal from birth-control pills. In many so-called idiopathic cases, when followed up for long periods, the patients are eventually found to have a prolactin-secreting adenoma, although in a number of cases no cause for the prolactinemia is ever found. Such cases need to be followed with sella tomography and CT scanning. Actually the most common type of galactorrhea is due to increased sensitization of the breast to normal circulating prolactin levels.

The last category of causes of hyperprolactinemia is that of central nervous system disorders. Neoplastic disorders in the area of the sella, such as parasellar tumors and ependymomas, can cause destruction of the hypothalamus and result in the hormonal changes, but not the spinal fluid changes, seen in this patient. Trauma in which the pituitary stalk is actually severed can also result in the same hormonal findings but again not the spinal fluid changes.

We are left with the last category, which is the group of inflammatory or infiltrative causes of hypothalamic disease. Two in this category are generally mentioned—eosinophilic granuloma and sarcoidosis. Eosinophilic granuloma can involve many organs, including the lung with interstitial disease, the bones with punched-out lesions, the hypophysis, and most commonly the posterior pituitary. But again, in the literature on eosinophilic granuloma, I could not find any evidence of spinal fluid changes such as were observed in this case.[5] The findings in sarcoidosis, however, are different, so I will discuss that condition since it seems to be the most likely underlying lesion in this patient.[6]

The brain is involved in about 10 percent of cases of sarcoidosis.[7] The central nervous system involvement actually occurs in the very early phases of the disease, whereas the peripheral nervous system infiltration and muscular involvement tend to occur later. Any part of the brain can be affected, but the most common areas are the cranial nerves, the meninges, the hypophysis and the pituitary. Of the cranial nerves, the facial nerve and the optic nerves are the most commonly affected. Patients with sarcoidosis may present with either unilateral or bilateral facial nerve palsy, so that the possibility of sarcoidosis should be thought of when such a condition occurs in a young person. Optic nerve involvement is generally missed, since simultaneous anterior and posterior chamber involvement of the eye may preoccupy the clinician's attention. The optic nerve may be infiltrated anywhere along its length by granuloma. Cerebral involvement can mimic a space-occupying lesion and can lead to mental changes. Meningeal involvement is common, with invasion along the basal leptomeninges, much like the spread of tuberculosis; such infiltration can affect the cranial nerves, hypophysis, and pituitary. Actually, pituitary involvement is most common, resulting in diabetes insipidus.

Involvement of the spinal cord with sarcoidosis is quite rare; only 17 cases were reported up to 1977. Myelography can be performed and may show partial block or signs of arachnoiditis; in this patient, however, the myelogram was negative. Demyelination of the posterior columns of the spinal cord can occur, as well as a mononeuropathy, a polyneuropathy, or a Guillain-Barré syndrome. The electromyographic findings are exactly as found in this case.

While discussing sarcoidosis, I should also mention tuberculosis. Tuberculosis can involve the leptomeninges; but tuberculous meningitis is a very difficult diagnosis to make. Patients with this condition tend to present in unusual ways, sometimes with cerebral findings and mental aberrations, also with cranial nerve involvement, but rarely with spinal cord involvement. I found some cases of pituitary destruction related to tuberculosis, but I could find no cases of hypophyseal destruction, which I believe to be the culprit in this case. The protocol here records spinal fluid changes exactly as would be found in tuberculous meningitis.[8]

Could this then have been tuberculosis? I would have been worried by the spinal fluid changes; although the PPD is usually positive with tuberculous meningitis, it can be negative in about 25 percent of cases. A smear of the spinal fluid is actually negative in 75 percent of the cases of tuberculous meningitis, so that would not help. We would have had to wait for the spinal fluid cultures.

How would I make a diagnosis of sarcoidosis in this kind of case? The anergy is supportive of the diagnosis of sarcoidosis. I reviewed 25 cases of sarcoidosis with neurologic involvement; in only about one half of the cases was the diagnosis made during life. Being a pulmonary specialist, I would have opted for a transbronchial biopsy, because someone was wise enough to request a gallium scan of the lungs. Gallium is not taken up by normal lung tissue, but it is taken up by neoplastic and inflammatory lung tissue, such as that of tuberculosis or sarcoidosis. The fact that gallium is present in abnormal amounts in this patient's lung would indicate an inflammatory process to me, consequently, my bias toward a transbronchial biopsy. One could also perform a biopsy on a peripheral nerve or muscle. Again I would caution that the finding of non-caseating granuloma is non-specific and that it could be present in tuberculosis. Once I had identified a non-caseating granuloma, and with these spinal fluid changes, I would have opted to treat the patient with steroids and, at the same time, with antituberculous therapy while waiting for the results of spinal fluid cultures. If the cultures were eventually negative, I would discontinue the antituberculous therapy and continue the corticosteroids.

In summary, I believe that this patient had sarcoidosis infiltrating the basal leptomeninges and hypophysis, as well as probably the optic nerve as suggested by the nasal field-visual defect. A pituitary lesion would be expected to produce bitemporal field findings, not nasal ones; but in this instance, I believe that the optic nerve itself was involved. I think the sarcoidosis extended into the meninges and also into the peripheral nerves of the lower extremities.

CLINICAL DIAGNOSES

Sarcoidosis, involving basal leptomeninges, hypothalamus, and right optic nerve.

Galactorrhea-amenorrhea syndrome secondary to sarcoidosis.

Peripheral neuropathy of lower extremities, secondary to infiltration by sarcoid tissue.

PATHOLOGY PRESENTATION

Dr Schwartzman: Someone on rounds noted that the patient had very prominent lacrimal glands. The diagnostic procedure referred to in the protocol was a biopsy of one of these glands.

Laura Molho, MD (Attending Pathologist, Queens Hospital Center; Assistant Clinical Professor of Pathology, SUNY School of Medicine at Stony Brook): Low-power views of the lacrimal gland biopsy specimen showed, within the otherwise normal structure of the gland, pale-staining, circumscribed infiltrates surrounded by lymphocytes (Fig 1). Under higher power examination, these areas were typical of non-necrotizing, non-caseating granulomas, surrounded by otherwise unremarkable glandular tissue (Fig 2). They consisted primarily of large epithelioid cells, admixed with giant cells and lymphocytes, without evidence of necrosis. The granulomas were numerous and all essentially similar in appearance. In the presence of granulomatous disease, special histologic stains to rule out tuberculosis are needed; the results in this case were negative. Other stains to rule out fungi were also negative.

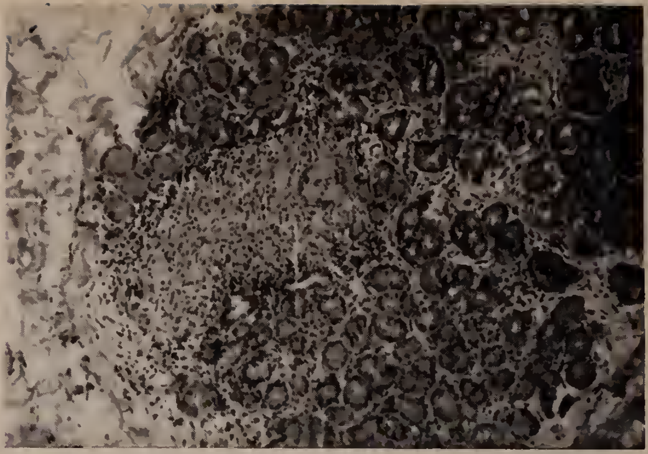

FIGURE 1. Non-caseating granuloma in lacrimal gland. Hematoxylin and eosin stain, original magnification × 100.

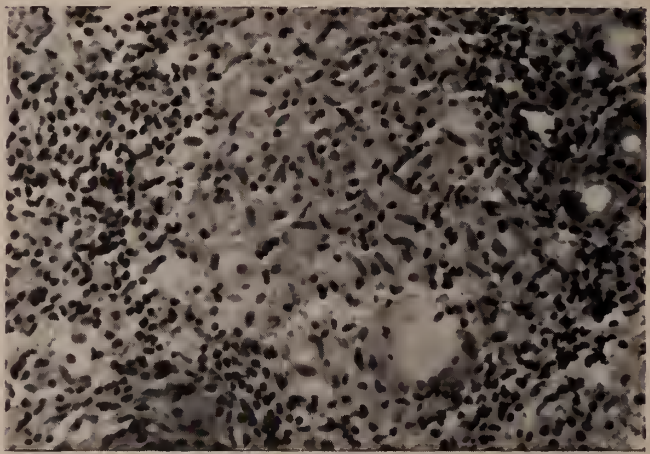

FIGURE 2. Detail of non-caseating granuloma (lymphocytes, epithelioid cells, giant cell). Hematoxylin and eosin stain, original magnification × 250.

Studies of conjunctival biopsy specimens have been made by various investigators; one such study at the Queens General Hospital Pulmonary Clinic included 60 cases of known sarcoidosis, 25 cases of tuberculosis, and 15 cases of various other pulmonary diseases.[9] Among the patients with known sarcoidosis, one third yielded positive conjunctival biopsy specimens with granulomas. None of the patients with tuberculosis showed granulomas on biopsy, nor did any of the remaining patients with other pulmonary diseases. So we do not expect that asymptomatic tuberculosis or asymptomatic fungus infection would involve the eye.

As pathologists, we are not usually able to make a definite diagnosis of sarcoidosis on histologic appearance alone[10]; but in this case, considering all the evidence at hand, I think we can safely state that our findings are compatible with sarcoidosis.

Howard Kolodny MD (Professor of Clinical Medicine, SUNY of Stony Brook): I would like to make two comments. First in connection with hypothyroidism, galactorrhea is most often associated with primary hypothyroidism. Prolactinomas are an uncommon cause of secondary (low TSH) hypothyroidism. When the TSH level is elevated in primary hypothyroidism, you may also see a simultaneous elevation in the prolactin level.

The use of sella tomograms in search of a cause of hyperprolactinemia has proved to be very unreliable since the incidence of false-positives is extremely high. When the sella is normal on plain x-ray film, hypopituitarism is extremely unusual in association with prolactinemia. The clinical information in this case would point to the central nervous system as the site of the underlying lesion.

The other point I would like to make is on the testing that was performed on this patient. The thyroid-releasing hormone (TRH) test is a measure of the integrity of the pituitary, whereas the insulin-induced hypoglycemia test has its major action on the hypothalamic area. When using these two tests, two different anatomic areas are being evaluated. The patient under discussion failed to respond to either test, suggesting both hypothalamic and pituitary involvement. It would have been very interesting to have a FSH/LH-releasing hormone study on this patient to document that the pathologic process involved both the hypothalamus and the pituitary.

Bruce Schneider, MD (Chief, Division of Endocrinology, LIJ-HMC): In hypothalamic-pituitary sarcoidosis, there are frequently disturbances of osmoregulation and of thirst, especially in those patients with lesions involving one or more anterior pituitary hormones. The disorders of osmoregulation and thirst can be attributed to the anatomic localization of the sarcoid granulomas within the hypothalamus. In addition, the granuloma itself, because of its increased angiotensin-converting enzyme activity, may generate local elevation of angiotensin II levels that have been shown, in experimental animals at least, to have an effect on water intake.

Marc Yunis, MD (Department of Medicine): The patient was also obese.

Dr Schneider: We have no details relating to the development of obesity in this patient prior to the onset of her symptoms. One would have to have evidence of rapid onset of obesity following the onset of her illness. If the granulomas involved the ventromedial hypothalamus, this could result in a hypothalamic obesity syndrome, at least theoretically. If they involved the lateral hypothalamus, it is conceivable that they could produce an anorexia-like syndrome with hypophagia and weight loss. There can also be disturbance of thermoregulation.

Kanti Rai, MD (Chief, Division of Hematology/Oncology, LIJ-HMC): Dr Steinberg, could you comment on the present status of the Kveim test?

Dr Steinberg: I did not mention the Kveim test because, looking at the protocol, it appears that there was some urgency in making the diagnosis. The Kveim test is a very valuable tool. To make a diagnosis of sarcoidosis, according to the classic definition as it was revised in the 1979 International Conference on Sarcoidosis, a positive tissue is required from more than one organ. But generally we are satisfied with the finding of non-caseating granulomas in one organ, together with the appropriate clinical picture. I think that the controversies that exist in the literature have resulted from the fact that different investigators have used different Kveim antigen, and cross reactivity has occurred with other diseases such as tuberculosis and Crohn's disease. If one uses the Kveim antigen used by Dr Siltzbach and his group, there is only a 2 to 3 percent false-positive reactivity in non-sarcoid patients.[11]

Also, it is important to remember that the longer the sarcoidosis has been present, generally the less positive the Kveim reaction. On the other hand, when lymph nodes are involved clinically the more positive the Kveim test. I do not know about the incidence of a positive Kveim test in neurologic sarcoidosis. Unfortunately, time was of the essence in this case and that is why I suggested the tissue biopsy.

I would offer a note of caution about some of the studies of extrapulmonary biopsies. I think that one has to be acutely aware of the fact that sarcoidosis varies greatly in different parts of the world, and sometimes even in different counties. The sarcoidosis that we see in eastern Queens County differs quite a bit from the sarcoidosis seen in the western portions of the county. A study conducted in a sarcoid clinic in western Queens would frequently uncover extrapulmonary sarcoid. A similar study conducted at this hospital would not.

Andrew Wachtel MD (Resident, Medicine): Could you comment on the chances of obtaining a positive transbronchial biopsy specimen from a patient with sarcoidosis whose chest film shows no abnormalities?

Dr Steinberg: I do not know the answer. You are referring to a stage 0 or stage I pulmonary sarcoidosis. In stage II, there is a 70 to 80 percent positive rate with transbronchial biopsy, which is probably the method of choice for diagnosing sarcoidosis.[12] Even though mediastinoscopy has a 95 percent positive rate, it requires general anesthesia and an incision, whereas transbronchial biopsy does not.

In interstitial lung disease of any kind, the chest film can show no abnormalities about 30 percent of the time. I am not aware of any studies that looked at Stage 0 or I sarcoidosis with transbronchial biopsy. My guess would be that the positivity rate would actually be very close to or the same as that of stage II sarcoidosis. If you look at this case, there is a positive gallium scan and an alveolar-arterial oxygen gradient, suggesting pulmonary dysfunction. The fact that the lesions are not visible on film means that they just have not reached visibility size, but I suspect that there would be interstitial and peribronchial disease anyway.

Dr Yunis: Dr Schwartzman, could you give us a further follow-up on this patient?

Dr Schwartzman: The patient was treated with synthroid, bromocriptine, and steroids, together with physical therapy. I last saw her about four months ago; at that time she was ambulating with the use of a cane only, and urinary incontinence had not developed. She has done well.

FINAL DIAGNOSES

Granulomatous disease of lacrimal glands, most probably sarcoidosis.

Probable widespread sarcoidosis infiltrating the lungs, basal leptomeninges, pituitary, hypothalamus, and peripheral nerves, with resulting galactorrhea-amenorrhea syndrome and severe peripheral neuropathy of lower extremities.

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FROM THE LIBRARY

RELIEF FOR TRAFFIC CONGESTION

The newspapers frequently print fanciful schemes to relieve traffic congestion in New York City, but the newspapers of October 6 described an actual demonstration that was so ridiculously simple that the man who tried it successfully was arrested for disturbing the peace simply because he drew an applauding crowd. *The New York Times* with its reputation for seriousness makes the following editorial comment on the incident:

> The authorities made a bad error in judgment when they committed to Bellevue yesterday the middle-aged negro caught running along Broadway near Forty-second Street on the tops of street cars, buses and taxicabs. The policeman who had him locked up says that he was out of work and took this unusual method of advertising the fact.
>
> But is this any indication that he is demented? On the contrary, he may be a genius. He may have discovered the solution of one of the most difficult problems with which the city is confronted. The gentleman should be referred to the Mayor's Committee on Plan and Survey, not to Bellevue.
>
> Congestion is terrible and growing worse. The air is full of schemes for double-decked streets and bridges for pedestrians. But these things are expensive and the city is poor. What if the pedestrians could be persuaded to give up the sidewalks altogether and trained to walk on top of the moving lines of vehicles?

NY State J Med 1928; 28:2054

The Personal Health Care System

A new proposal for a national health program

STEVEN JONAS, MD, MPH

ABSTRACT A new proposal for a national health services system is based on an analysis of population health, health-services needs, and health care delivery system problems. Called the Personal Health Care System (PHCS), it uses a time-honored approach to achieve stated goals and objectives: the contract. Through it, planning and financing functions are intertwined. Government is the money raiser and contract writer. As contractors, providers maintain their independent status. Desired health care program outcomes can be specified in the contracts. Consumer boards can play an important role in assessing contract compliance using program outcome measures. The proposal's advantages, in addition to focusing on needs and outcomes, include a fostering of competition with significant opportunity for cost containment and maintenance of provider independence.

(NY State J Med 1984;84:187–189)

INTRODUCTION

> The problem of providing satisfactory medical service to all the people of the United States at costs which they can meet is a pressing one. At the present time, many persons do not receive service which is adequate either in quantity or quality, and the costs of service are inequably distributed. The result is a tremendous amount of preventable physical pain and mental anguish, needless deaths, economic inefficiency, and social waste. Furthermore, these conditions are, as the following pages will show, largely unnecessary. The United States has the economic resources, the organizing ability, and the technical experience to solve this problem.[1]

This trenchant paragraph is not a current review of the problems and prospects of the United States health care delivery system but the final report of the Committee on the Costs of Medical Care, published in 1932. This paragraph is still wholly correct and applicable to the present reality of the United States health care delivery system. The only change is that there are additional major problems that one can identify and add to the list: (1) we do nowhere near what we could do in the realm of health/promotion/disease prevention; (2) costs are now astronomical and increasing at a rate that far surpasses inflation; (3) medical manpower is poorly distributed by specialty and geography; (4) institutional care is not utilized in an efficient manner; (5) equity has not been achieved.

This list of problems is well known and has been attested to over the years by many authorities.[2–4] Solutions to the list of problems have been proposed many times although perhaps not with the same frequency as the problems arise. Nevertheless, no comprehensive, national program designed to deal with the problems has yet been enacted or implemented. To be sure, various attempts to deal with components of the list of problems have been made. These include the development of private health insurance, the Hill-Burton Act, Federal support for biomedical research and health sciences education, Medicare/Medicaid, various approaches to health planning, attempts to control hospital capital formation, hospital rate-setting, the decline in the use of long-term care institutions for mental health services, government support of group practice development, and required peer review of medical quality and utilization. These efforts have been piecemeal, however.

For years, proposals to establish a comprehensive, national program have been made. National health insurance (NHI), in one iteration or another, is a concept that has been around for a long time.[5] More recently, several proposals for a United States national health service (NHS) have been developed,[6] and most recently, the Consumer-Choice and Pro-competition proposals appeared.[7–9] In this paper, following a brief analysis of NHI, NHS, and competition, a new idea called the Personal Health Care System (PHCS) is presented.

COMPETITION, NATIONAL HEALTH INSURANCE AND NATIONAL HEALTH SERVICE

Competition seems to have become the common word in the arena of health care delivery systems in the 1980s. As a proposal it has taken a number of forms. The most prominent to date has been associated with the name Alain Enthoven,[10] and is based upon the notion that individual choice in expenditure can influence the direction of the health care delivery system. It has been criticized by many.[11–14] It rests on a limited concept of competition, a concept that does not recognize the reality that patients, as buyers of medical care, often have too little knowledge and

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Address correspondence to Dr Jonas, Associate Professor, Department of Community and Preventive Medicine, State University of New York at Stony Brook, Stony Brook, NY 11794

effective power of choice to influence price, availability, and quality. Thus it is saddled with a flawed basic principle. Furthermore, it focuses on the administrative processes of regulation and cost containment. It does not face the many substantive problems in program outcomes confronting the health care delivery system: distribution of services, types of services, manpower supply, physical and financial access, quality of care, and equity. (The terms "process" and "outcome" are *not* being used in the Donabedian quality assurance sense but rather to refer to administrative mechanisms (processes) and programmatic desiderata (outcomes) in terms of improved health and more efficient use of resources.)

National health insurance in any form is primarily a method of financing and paying for health services. Most of its variants would achieve equity; however, it could deal only indirectly with the other non-financial problems. A government-owned and operated national health service could deal with the whole problem-list directly. However, government operation of health services is a field in which the United States for the most part has a poor track record. If for no other reason, therefore, NHS cannot be supported. (Political feasibility of one proposal or another is not being used as a criterion upon which to rate its merit. It is quite obvious from the history of the United States health care delivery system that *any* major restructuring will face very tough political sledding.)

The Conceptual Basis of the Personal Health Care System

In considering and discarding NHI, NHS, and the Enthoven approach as possible solutions, certain parameters for a useful alternative have been established. Ownership and control of health facilities and manpower should remain in private hands as they are now. The principal focus of any new approach should be on solving system-wide health and health services problems. To do this, the planning, financing, and operating systems should be linked. Goals and objectives for problem-solving should be clearly established. Program outcome regulation rather than administrative process regulation should be the principal regulatory approach. Good performance in terms of achieving goals should be rewarded, whereas unsatisfactory performance should not, and could be penalized.

The PHCS recognizes that in the United States market forces operating in a controlled environment may be able to solve problems, the solutions of which in other countries are approached through more modern, direct program planning and operation. It makes the assumption that competition can be effective in achieving substantive goals. However, it recognizes that competition can take different forms and that to be effective the competition process requires informed buyers and informed sellers. PHCS then goes on to conclude that competition cannot solve problems in the health care delivery system if it relies on individual users of services as its principal buyers. The nub of the PHCS is the creation of informed buyers who can act on behalf of consumers in a manner that links planning, financing, and operations. It does this in a flexible manner by using a traditional American approach to problem-solving: the contract.

How the PHCS Would Work

Under the PHCS the Federal government would be responsible for raising all the money to pay for health services, from a combination of employer/employee contributions, special and general tax revenues, and certain direct user payments—the current sources of funds for the health care delivery system. Health insurance premiums paid at present to private insurers would go to the PHCS. Available funds would be distributed across the nation by state or region or both. The state/regional allotments would be based on past experience and future projections of need. After a cooperative effort in establishing specifications, agents would be designated to negotiate contracts with health care providers to deliver the specified services. These agents could be state governments, local governments, new regional health authorities, health insurance companies, or some combination of the above.

All existing health care providers would be free to bid for the contracts. Most areas of the country would have two or more active contractors, so people would have a choice for care. Individuals would have to choose one contractor for some minimum set time, but would be allowed to change periodically. Contractors could be paid through a combination of lump sum and capitation payments or some form of the Diagnosis Related Group system, applied to both institutional and individual providers. Item-of-service payments would not be used by contracting agencies, although contractors would be free to pay providers on a fee-for-service basis. Contract enforcement would be carried out by the contracting agencies which could be assisted in that function by consumer boards. Use of this option would enable meaningful consumer participation in the health care delivery system, focusing on outcomes. Since everyone in the country would be covered by contract services, equity would be achieved.

The key to resolving the problems spelled out above is the creative use of contract specifications and enforcement procedures. These could be used to increase the level of health promotion/disease prevention services, emphasize primary and ambulatory care, control utilization, improve medical quality, alter the geographic distribution of services, rationalize the distribution of labor, control the use of new technologies, improve accessability, availability, and acceptability, encourage coordination, and control capital formation. There is, of course, no guarantee that all or any of these things would happen. Under the contract mechanism the system certainly could continue to function in the same old way. But the potential for positive change would be there without government ownership or regulation of administrative process. The focus would, or at least could, clearly be on problems and programmatic outcomes.

The PHCS is goal-oriented. It has a regulatory function, but the regulations focus on service needs and program outcomes, as did the health-planning guidelines issued in the last days of the Carter administration and subsequently rescinded by its successor.[15] It introduces real, effective competition, fostered by the use of knowledgeable agents buying services on behalf of the public. It closely links planning, financing, and operations, something that must be done if the stated goals are to be solved without imposing a straitjacket of direct government ownership and operation.

PREDECESSORS AND IMPLEMENTERS

The Personal Health Care System is a concept built upon a foundation of earlier experience. It draws upon this country's 50-year experience with pre-paid group practice. It has certain features in common with an old American Hospital Association NHI proposal called Ameriplan.[16] The germ of the PHCS concept was first developed during a 1975 study of a contract-based system operated by the New York State and City governments in the 1970s to pay for voluntary hospital out-patient services provided to the poor in New York City who are not eligible for Medicaid.[17] That system used lump-sum payments under contracts that contained detailed performance specifications and provided for joint health department/community council review of performance. It demonstrated that the contract mechanism could be used to pay for services and improve their quality at the same time.

In 1982 certain changes began taking place in the health care planning and financing system in several parts of the country; these changes include some major features of the PHCS. Arizona, the only non-Medicaid state, is implementing a contract-based system to care for its poor.[18] On a grander scale, California is in the midst of developing a contract-based program for its entire Medicaid population.[19-21] Insurance companies in the state also have been given the authority to pay for care for their own beneficiaries by contracting directly with providers to deliver a specified set of services.[22] This latter system is a more comprehensive version of the Preferred-Provider Option plan, which a number of insurance companies are implementing in various parts of the country.[23]

Massachusetts has gone to global budgeting for all of its hospitals.[24-25] In the fall of 1982 the Health Care Financing Administration made grants to five states for Medicaid demonstration projects, each of which has some features in common with the PHCS proposal.[26] Alvin Tarlov, chairman of the Graduate Medical Education National Advisory Committee, has predicted that in the future "most physicians will be practicing within a corporate structure and that a large fraction of their income will derive from prepaid capitation contracts."[27] In addition to the government and insurance companies, the private sector is also beginning to show interest in this approach. The Chrysler Corporation, in cooperation with the United Automobile Workers, is implementing a fixed-fee contract program for its workers, developed for it by a committee chaired by former Health, Education, and Welfare Secretary Joseph Califano.[28] Thus, the PHCS concept appears to be consistent with certain trends that have been developing in the United States health care delivery system in recent years.

CONCLUSION

The United States health care delivery system has faced serious problems for many years. The system may break down in the forseeable future as some observers predict. The case for change, however, does not rest on the threat of breakdown, but rather on economic factors, political and social considerations, rationality, and professional imperatives to do a good job for its own sake. The first question to be asked is: does something really need to be done? Second, should an alternative system be created? These questions and their answers are matters of belief, not science. No alternative will be perfect; each will create its own problems.

The PHCS offers no more of a guarantee of success than can NHI, NHS or the Enthoven approach. The belief is that it focuses on identified problems, has the ability to solve them, and is consistent with American experience. In addition, it is thought that the new problems it creates are for the most part soluble and that, assuming appropriate funding, organization, and leadership, its ability to focus on system goals and objectives outweighs its disadvantages.

It would appear that the PHCS concept is worthy of further development and consideration as an alternative to current proposals.

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A SIMPLE METHOD OF TUBAL STERILIZATION

ELIOT BISHOP, MD, WM. F. NELMS, MD

(*Reprinted from the* New York State Journal of Medicine, *1930; 30:214–216*)

This brief paper which we will illustrate by pictures, still and moving,* is purely one of technic. The subject of sterilization in its broad aspects—moral, ethical, social and medical has been handled by abler pens than ours. Two of the most recent are by Williams[1] in the *Journal of the A. M. A.* for Oct. 27, 1928 and by Dickinson[2] in the *New York State Journal of Medicine*, May 15, 1929. Neither will this paper take us through the history of even the technical aspect, though we will append some bibliography of the results of different methods.

To return—any surgical procedure should exhibit three principles which we will align alliteratively: Simplicity, Safety, Security. We can easily demonstrate to you that the procedure which we present is *simple.* It would seem also as though it must be accepted as one which is as *safe* as any invasion of the peritoneal cavity. As to *surety*, we will state that there is no known case of ours that has become pregnant.

Taking up each aspect separately, we want to state that its extreme simplicity has possibly kept it from becoming more popular. Our earlier work followed that originated by the late August Hussey which buried the cut stump of the tube and also covered the raw area in the broad ligament and the uterine cornuum with a combined ligature and suture ingeniously applied. No pregnancy followed its use as far as is known, but at times annoying bleeding occurred necessitating complete salpingectomy for its control.

The method we are advocating we first saw in the hands of the late Ralph Pomeroy who made no claim for originality but stated that he had never seen it done. Its simplicity lies in the fact that it is nothing more or less than that a loop in the loose, middle portion of the tube is ligated with *absorbable* suture material and resected. It takes but a few seconds during a laparotomy and usually no longer by vagina. Its similarity to and its difference from Madlener's method we will refer to later.

So much for simplicity. As to safety, hemorrhage and infection are yet to be feared in any operative procedure. As to the latter, the chance of latent infection being present has scarcely entered our heads, for a tube to be functioning is presumed to be healthy and non-infecting. However, if desired, the cut ends may be cauterized by heat or a chemical. As to hemorrhage, the vessels that are apt to be involved are ligated before section, so there ought to be only a few drops of blood loss. By the vaginal route there is some chance of laceration of the tube during its delivery, but no more than in any other vaginal method of tubal sterilization. We feel that we must be supported in our contention of simplicity and safety.

As to surety, more proof will be needed and that is not so easy. Incomplete as this report may be, we are bringing it forth to stimulate more use of this method so that it justly may be followed or condemned. In what way does this procedure give assurance of sterilizing? The first critical thought is that we use absorbable suture material, which indeed we do, our practice having been to utilize a double strand of No. 1 chromic catgut. No absorption occurs until there is no fear of bleeding and when it does the two cut ends draw apart as we have noted in two subsequent laparotomies and we will show on one of our experiments. During this period the plastic exudate of the peritoneum has been thrown out and become organized, and here is the secret of the process. Nature throws over a barrier of new peritoneum and it becomes a permanent one with no chance, we feel confident, of fistula formation.

We definitely do *not* crush the tube first as has been advocated by Madlener and others, for the crushed tissue may open a way for fistula formation; we definitely do *not* use non-absorbable ligature material as that very material, we fear, might slough through and a fistula develop. Nature through her eliminative mechanism tends to absorb a disused organ and we feel in this procedure that the two portions of each tube steadily shrink up to a narrow strand even possibly closing the lumen. We will show a slide of an x-ray picture of a uterus whose tubes have been ligated and two years subsequently injected with sodium iodide and the material does not leave the endometrial cavity.

As to clinical results, as near as our records can be found we have done this about 60 times, there being no record of a pregnancy. Follow-up by letter and telephone has given us, as far as we have been able to achieve it, no report of a pregnancy and no use of contraceptives. A personal communication with Dr. R. M. Beach supplements this with about 40 additional cases with no reported pregnancies. On a dozen animals—guinea pigs and cats—which are known to be prolific and with frequent periods of rut, we also have found no pregnancies.

From the Department of Gynecology and Obstetrics of The Brooklyn Hospital.

* Read at the Annual Meeting of the Medical Society of the State of New York, at Utica, NY, June 6, 1929.

In reviewing the literature of this subject there are so many various methods of operation which have been used that we will not have space enough to include them all. We are concerned only with those performed upon the Fallopian Tubes as this is the title of the paper. One is struck by the great number of failures reported following all kinds of tubal ligations and resections, but it is interesting to note that the material used in the vast majority of these cases has been a *non*-absorbable suture—usually silk.

Littig[3] gives a thorough survey of the literature of this subject up to 1912 citing all of the methods used up to that time and shows the discouraging fact that failures have occurred with all of them. He concludes: 1—that animal experiments, the ligation or excision of pathological tubes, and the results of like operations on normal tubes prove conclusively that tubal ligation with or without excision is not an efficient measure to prevent conception; and 2—the only operation which gives promise of success is excision of all or a part of the tube with a deep, wedge-shaped excision of the uterine cornu, including the pars uterina of the tube, the defect to be closed with a musculo-muscular and a seroserous row of sutures.

Some of the most commonly used methods reported since the above article are:

1st. By Kohler[4] who loops the tube in its middle portion, ligates with silk sutures and cuts off the loop.

2nd. By Peitman[5] who ligates the tube with silk in two places about two cm. apart, splits the peritoneum exposing the tube, excises a section of the tube between the ligatures and then sews the split peritoneum over this with fine silk sutures. He calls this "Subserous partial tubal extirpation."

3rd. By Rabinowitz[6] who does just as Peitman except that he sews the ends of the cut tubes with silk and buries the uterine stump in the musculature of the uterus.

4th. By Planner[7] who ligates doubly with silk, cuts between the ligatures, sews the ends with silk and buries the uterine stump in the broad ligament.

5th. By Hofbauer[8] who cuts the tube, ligates the proximal end with silk and approximates the round and ovarian ligaments over the stump.

6th. By Madlener[9] who loops the tube, crushes it together with the mesosalpinx and ligates with silk or cat-gut sutures.

7th. By Williams[10] whose routine method is to excise the proximal end of the tube from the uterine cornu by a wedge-shaped incision, carefully closing the wound with fine sutures.

As to results we have been unable to find statistics showing the number or percentage of failures for each specific method used. According to Kohler[11], 21 cases of pregnancy after tubal sterilization have been reported in the literature, most of these having been collected by Nurnberger. Sarkissiantz estimates the failures after bilateral ligation and resection at 1:3000. On the basis of cases reported in literature 6.5%. In Doderlein's Clinic from 1908–1918, 67 tubal sterilizations were performed with 4 failures or about 5.97%. Failures after single or double ligation of the tubes according to Kalliwoda's calculation (based on 75 cases collected from the literature) numbered 14 or 1/5 of the cases.

Madlener[9] reported 89 cases by his method all of which were successful.

Von Waser[12] reported 225 cases sterilized by Madlener's method with one failure. In 1926, 39 cases had been added to Madlener's first series making in all, excluding 4 deaths, 124 cases with no failure. Keller reported that of 15–20 cases operated on by Madlener's method only one failed. Schreiner[13] reports 142 sterilizations by Madlener's method with no failures. Nurnberger[14] reports 6 or 7% failures following the operation in which a wedge at the horn of the uterus is removed.

In conclusion, while we can not state positively that sterilization by our method will give a better percentage of results than those reported above, we believe so for the following reasons:

1. In a series of 100 cases no known pregnancies have occurred.

2. Our use of absorbable suture material is not as likely to cut through the stump.

3. The fact that we have seen (in subsequent laparotomies and in experimental cats) that the two cut ends of the tube have separated and become covered with peritoneum.

4. Sodium iodide tubal patency tests have shown the fluid to be confined to the uterus with none in the peritoneal cavity.

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Isolated spontaneous fallopian tube torsion diagnosed by laparoscopy and ultrasonography

PATRICIA JOSEPH, MD, ROSALYN KUTCHER, MD, SYLVAIN KLEINHAUS, MD

Torsion of diseased uterine adnexa is a well-recognized clinical entity. Isolated torsion of a normal fallopian tube without involvement of the ovary or preexisting disease is a rare finding. We report such an instance, in which the tubal torsion was seen as a fluid-filled mass on ultrasonography and diagnosed correctly at laparoscopy, prior to laparotomy.

CASE REPORT

A 14-year-old girl was admitted to the hospital because of worsening abdominal pain. Menstruation had begun at age 12; two months prior to the onset of menses the patient had her first episode of severe lower abdominal pain. At that time she was admitted to the hospital for observation, and her symptoms resolved spontaneously over the course of several days. During the next two years she had multiple episodes of similar pain and was hospitalized a second time. One year before this admission her symptoms again resolved spontaneously. Results of a barium study of the upper gastrointestinal track during her second hospital stay were reported normal. Eight days prior to this admission the patient began to experience mild, intermittent pain in the right lower quadrant, which became acute and was associated with two episodes of bilious vomiting. She denied any change in bowel or bladder habits, and had her last menstrual period four weeks before admission. Her past medical history was otherwise noncontributory.

On physical examination she was afebrile, and her abdominal examination revealed active bowel sounds with mild tenderness and questionable rebound in the right lower quadrant, but no guarding. On examination by a gynecologist, no pelvic abnormality was noted other than mild right lower quadrant tenderness. Her WBC count was 16,400/mm^3. Her abdominal pain continued and a low-grade fever developed. The right lower quadrant tenderness with equivocal rebound and guarding persisted. The WBC count increased to 18,300/mm^3 with a shift to the left. Possible diagnoses of appendicitis, torsion of an ovarian cyst, and Crohn's disease were considered. Ultrasonography of the pelvis revealed a septated, fluid-filled mass distinct from the right ovary, lying behind the uterus in the cul-de-sac and below the ovary (Fig 1). A presumptive diagnosis of torsion of a paraovarian cyst was made, and the patient was taken to the operating room.

On laparoscopic examination of the abdomen and pelvis, the uterus and left tube and ovary were normal, with the exception of a 1-cm ovarian cyst. The right fallopian tube was normal for a distance of 1.5 cm from the uterus, but then appeared to be twisted and tucked into the cul-de-sac, where a bluish, cyanotic mass was visualized (Fig 2). The right ovary could not be seen at this time, but the appendix was inspected and no evidence of acute inflammation was found. A formal laparotomy through a Pfannenstiel incision was then performed. The right fallopian tube was twisted at least 720°, grossly distended, and completely infarcted. The right ovary appeared completely normal, and a right salpingectomy and incidental appendectomy were performed. The pathology report showed "fallopian tube with hemorrhagic infarct, hematosalpinx, and fibrinous perisalpingitis (secondary to torsion in proximal segment)" (Fig 3). Postoperative recovery was uneventful.

DISCUSSION

Torsion of the uterine adnexa is a clinical entity that was first described by Sutton in 1890,[1] with many cases reported since that time. The torsion usually involves both the fallopian tube and the ovary,[2-7] whereas isolated torsion of the tube is rare.[7,8] In most cases, the isolated tubal torsion is associated with other conditions that have in some way altered the pelvic anatomy. These conditions can be classified into five categories: (1) cysts and tumors: ovarian,[9,10] paraovarian,[11,12] tubal tumors,[13] and uterine fibroids[10]; (2) previous surgery; Pomeroy sterilization[14]; (3) pregnancy[10,15,16]; (4) infections: acute and

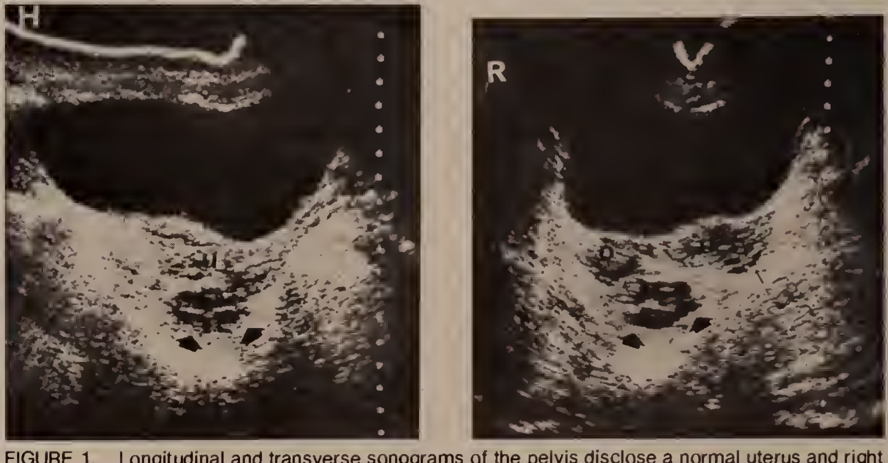

FIGURE 1. Longitudinal and transverse sonograms of the pelvis disclose a normal uterus and right ovary. In the right adnexa there is an elliptical fluid-filled mass with septation representing the twisted hematosalpinx (arrowheads). A small amount of fluid is present around the uterus and ovary (arrows). The left ovary was visualized at a more cephalic level. Abbreviations: H, head; R, right; U, uterus; O, ovary.

From the Departments of Surgery (Drs Kleinhaus, Joseph) and Radiology (Dr Kutcher), Montefiore Hospital and Medical Center-Albert Einstein College of Medicine, Bronx, New York.

Address correspondence to Dr Kleinhaus, Associate Professor of Surgery, Department of Surgery, Montefiore Hospital and Medical Center, 111 East 210th St, Bronx, NY 10467.

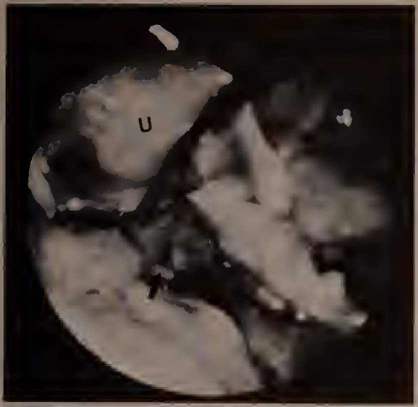

FIGURE 2. Laparoscopic picture shows a normal uterus and proximal right fallopian tube with torsion of the distal cyanotic segment of the tube (arrow).

chronic salpingitis[12,17] and tuberculous salpingitis[11]; (5) congenital abnormalities: unusually long or absent mesosalpinx,[11,13] and elongated fallopian tube.[12]

The symptoms of isolated tubal torsion are vague and variable and frequently mimic appendicitis, renal colic, pelvic inflammatory disease, and torsion of ovarian cysts. Although nausea and lower abdominal pain are almost always present, vomiting, fever, and leukocytosis are inconstant findings. Because of the rarity of the disease and the nonspecific nature of the signs and symptoms, the correct diagnosis is rarely made before surgery. In a review of the literature in 1937 Blum and Sayre[17] noted 14 cases of isolated tubal torsion, in which the ipsilateral ovary and contralateral adnexa were normal. A review by Regad[18] in 1933 documented approximately 200 cases. Since then numerous other cases of isolated tubal torsion have been reported. In 1962 Blair[2] reviewed over 70 additional cases in the world literature; however, whether or not any of the previously mentioned predisposing conditions were present is not clear in many of these cases. The correct diagnosis was not made prior to laparotomy in any of the cases.

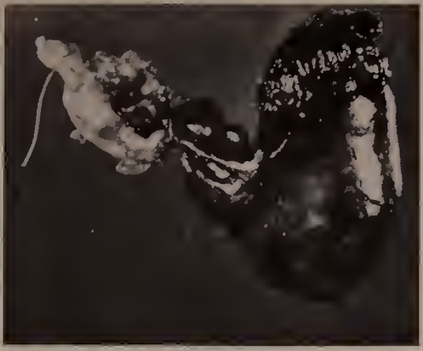

FIGURE 3. Pathologic specimen shows infarcted hemorrhagic right fallopian tube.

In the past decade, two new diagnostic methods, ultrasonography and laparoscopy, have come into more widespread use. The use of ultrasonography to visualize pelvic disease is well demonstrated in this case of isolated tubal torsion. Only one case has been reported previously, in which a cystic dilatation in the adnexal region, corresponding to a tubal torsion, was documented by ultrasonography before the operation. It is not clear, however, if the correct diagnosis was made prior to laparotomy.[19] Although hematosalpinx was one of several possible diagnoses considered, the definitive diagnosis was not made until laparoscopy was performed. This method has been especially useful in the evaluation of abdominal pain in adolescent girls, as demonstrated by one of us (S.K.).[20] In that case the pelvic anatomy and appendix were easily inspected, the correct diagnosis was made, and the patient underwent laparotomy. Had no significant pathologic condition been identified, a major operative procedure would have been avoided.

Since the correct diagnosis of tubal torsion is usually made late in the course of the disease, the tube is often already infarcted at the time of laparotomy; only rarely has tubal torsion been treated without the necessity of a salpingectomy.

The case presented here demonstrates the usefulness of ultrasonography and laparoscopy as adjunctive diagnostic techniques in the preoperative evaluation of abdominal and pelvic pain. Earlier and more aggressive use of these two relatively new diagnostic methods may, in the future, permit diagnosis and treatment of diseases, such as early tubal torsion without infarction, without subjecting the patient to laparotomy.

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Spontaneous amputation of the adnexae

A rare cause of prepubertal pelvic mass

EVA CHALAS, MD, WILLIAM J. MANN, MD, ZEV ROSENWAKS, MD,
CYNTHIA KAPLAN, MD, MARTIN WINICK, MD

A pelvic mass in a prepubertal female is an ominous finding.[1] Physiologic ovarian cysts rarely occur in this age group, and the differential diagnosis is essentially that for ovarian neoplasms. Furthermore, in this age group, malignant germ cell tumors are common and have had an exceptionally poor prognosis.

We encountered a six-year-old girl with a three-month history of urinary symptoms who was found to have a calcified pelvic mass on intravenous pyelogram (IVP). She was thought to have an ovarian tumor, but surgical exploration revealed calcification of adnexae that had undergone spontaneous amputation.

This syndrome is extremely rare, and has been reported primarily in the radiologic literature. We present this case to call the attention of pediatricians, general surgeons, gynecologists, and family practitioners to this benign condition which can appear as a prepubertal pelvic mass and for which no further therapy is required.

CASE REPORT

A six-year-old girl was brought to the University Hospital, State University of New York at Stony Brook, with a three-month history of dysuria, frequency, nocturnal enuresis, and sharp, intermittent suprapubic pain. Previous cystoscopy, cystogram, and urethral dilation failed to explain or relieve the child's symptoms. The child was delivered by a repeat cesarean section after an uncomplicated pregnancy and had normal growth and development.

Physical examination was unremarkable. Urine cultures and urine analysis were negative. An IVP revealed normal kidneys, ureters, and bladder. Incidental note was made of calcification in the pelvis, thought to be fecal. Urine cultures continued to be negative, and multiple urine analyses were normal.

A repeat IVP revealed a normal urinary tract, with an ovoid calcified mass in the right side of the pelvis. Results of physical examination were normal except for rectal examination which revealed a 3-cm mobile, nontender pelvic mass. Ultrasonography revealed an enlarged right ovary but failed to identify the left ovary. No calcification was seen on sonography.

The diagnosis of a germ cell neoplasm of the ovary was considered and the child was admitted for exploratory laparotomy. Chest x-ray films were normal, as were complete blood count with differential and values for liver enzymes, BUN, and creatinine. Alphafetoprotein and beta subunit human chorionic gonadotropin were undetectable in the patient's serum and a 46XX karyotype was confirmed.

At laparotomy, the right ovary was easily located and contained a 1-cm cyst, which was shelled out. The uterus appeared normal for a prepubertal child. There was no left ovary, and the distal fallopian tube was absent with no visible fimbria (Fig 1). A hard, 2 × 2 × 1-cm mass was found lying free in the cul-de-sac (Fig 2). Frozen section of this mass revealed fibrosis and calcification (Fig 3). Incidental appendectomy was performed. The patient did well after surgery and was discharged home. She had an uneventful recovery, returned to school, and is without symptoms at 24 months.

DISCUSSION

To the best of our knowledge, spontaneous ovarian amputation has not been previously reported in the general medical literature. There have been rare cases presented in pediatric and radiologic publications of prepubertal patients with calcified masses, who at laparotomy were found to have amputated adnexae and free-lying calcified pelvic masses.[2,3] Congenital anatomic defects are speculated to be responsible for torsion of the undiseased adnexae. A longer, more tortuous, or more mobile tube has been implicated in the literature as a possible cause.[3-6] Decreased restriction of movement by supporting structures may also play a role and may explain the higher incidence of the right fallopian tube torsion,[6] since the sigmoid colon may limit motion on the left.

Although the clinical experiences with spontaneous ovarian amputations are limited, urinary tract symptoms are often noted.[6] Our patient had dysuria, frequency, and suprapubic pain that resolved after laparotomy. The fact that the mass was calcified suggests that the process of infarction occurred long before and could not explain the patient's recent symptoms. The location of the mass at laparotomy also did not satisfactorily explain the presenting symptoms, although irritation of the bladder by the mass cannot be ruled out.

The frequency of torsion and amputation of the adnexae in children with vague abdominal pain cannot be estimated. In the adult population, the incidental finding of absent adnexae and calcified pelvic mass at the time of laparotomy has not been reported.[7,8] The recognition that this entity exists may

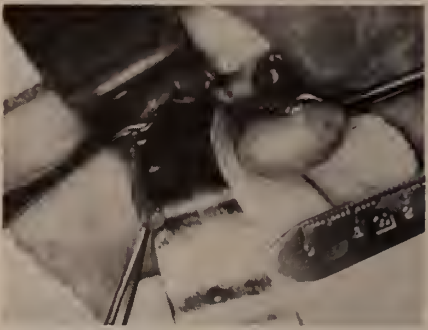

FIGURE 1. Intraoperative findings, with absent left ovary and distal left fallopian tube.

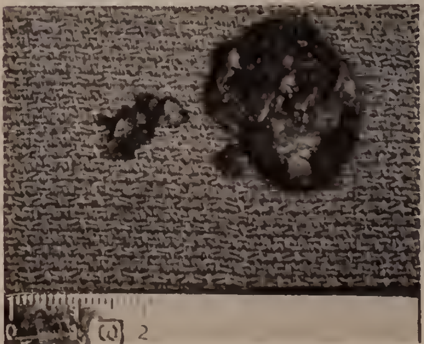

FIGURE 2. Hard 2 × 2 × 1-cm mass found lying free in the cul-de-sac.

From the Departments of Obstetrics and Gynecology (Drs Chalas, Mann, and Rosenwaks), Pathology (Dr Kaplan), and Surgery (Dr Winick), State University of Stony Brook, Stony Brook, NY.

Address correspondence to Dr Mann, Director, Division of Gyn Oncology, Department of Obstetrics and Gynecology, SUNY-Stony Brook, Stony Brook, NY 11794.

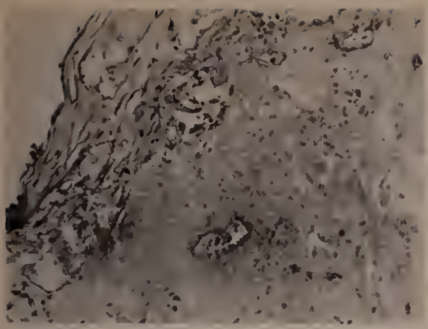

FIGURE 3. Mesothelial capsule in necrotic central portion with identifiable follicular oocytes and stromal cells.

further define the frequency.

Once the diagnosis has been established at surgery, no further therapy is indicated, and the child may be expected to have a normal reproductive life. It must be emphasized that it is not appropriate to make this diagnosis without exploration, since the rarity of this syndrome means the majority of prepubertal pelvic masses will be ovarian neoplasms.

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Nontraumatic clostridial myonecrosis and mycotic aneurysm formation

LAWRENCE SEMEL, MD, WILLIAM O. AIKMAN, MD, FREDERICK B. PARKER, JR, MD, MEHDI A. MARVASTI, MD

Mycotic aneurysm formation is an unusual complication of septicemia. Nontraumatic clostridial myonecrosis is also uncommon and its association with neoplastic disease has been reported to be high.[1] We recently treated a patient with spontaneous clostridial myonecrosis in the setting of an occult colon carcinoma in whom a mycotic aneurysm of the thoracic aorta subsequently developed, resulting in her death. The unusual nature of both entities prompted us to report this case.

CASE REPORT

A 60-year-old woman presented to the Emergency Room with a three-day history of progressive pain in the right leg. She was previously healthy, and there was no history of trauma, diabetes mellitus, or cardiovascular disease. Bowel habits were unchanged. Examination revealed an acutely ill woman with a pulse rate of 120/min, blood pressure 90/60 mm Hg, temperature 37°C and respirations of 30/min. Abdominal findings were within normal limits, and test results for occult blood in her urine were negative. The right leg was tense, cool, and mottled distal to the knee, and crepitus was present in the thigh. There were no pulses below the femoral level. Radiologic examination revealed gas in the soft tissues of the right leg and in the mediastinum outlining the aortic arch (Fig 1). White blood cell count was 37,000/mm^3 and blood glucose was 620 mg/dl. Aspiration of calf muscle returned watery brown fluid that revealed gram-positive bacilli and absence of white blood cells. A diagnosis of gas gangrene was made.

After fluid resuscitation, a high above knee guillotine amputation was performed. Gas was present within the muscle. Cultures of the muscle as well as preoperative blood culture grew *Clostridium septicum*. Antibiotic coverage was begun prior to surgery and continued for two weeks after surgery.

The patient recovered without evidence of extension of the myonecrosis beyond the amputation site. Postoperative chest x-ray showed that the mediastinal air had resolved. Repeat chest x-ray film revealed an enlarging cardiac silhouette; one week after amputation, pericardial drainage was performed for a sterile pericardial effusion. This was interpreted as representing a nonspecific pericarditis.

Despite lack of symptoms, a barium enema was performed in search of occult colon carcinoma. This demonstrated a nonobstructing carcinoma in the transverse colon, believed to be responsible for the initial Clostridium bacteremia that then seeded the right leg causing myonecrosis.

During preparation for elective colon resection, the patient became febrile, and a blood culture again revealed *C septicum*. Antibiotic therapy was reinstituted. A repeat chest film revealed mediastinal widening, and aortography showed an aneurysm of the transverse aorta extending proximally to the ascending aorta (Fig 2). Because of concern that the colon lesion might be a source of bacteremia that could infect an aortic prosthesis, colon resection was initially performed to be followed later by aneurysm resection. This sequence allowed evaluation of the extent of the carcinomas as well. Resection of the aneurysm was not to be performed in the face of metastatic disease. A Duke C adenocarcinoma was resected with primary anastomosis performed. Blood pressure and car-

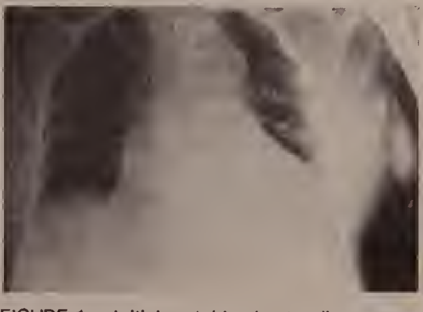

FIGURE 1. Initial portable chest radiogram revealing gas in the mediastinum outlining an area of calcification in the aortic knob. A cvp catheter and an endotracheal tube are in place.

From the Department of Surgery, Upstate Medical Center, 750 East Adams Street, Syracuse, New York 13210.

Address correspondence to Dr Semel, Resident, Department of Surgery, 750 East Adams Street, Syracuse, New York 13210.

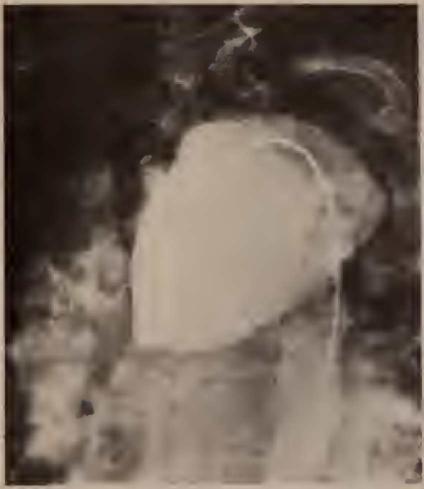

FIGURE 2. Aortogram showing large aneurysm of aortic arch. The catheter tip is in the lumen of the aneurysm.

diac contractility were controlled with nitroprusside and propranolol. Twenty hours after surgery, cardiac arrest occurred. Resuscitation was unsuccessful.

Postmortem examination revealed a very large aneurysm involving the ascending aorta and transverse arch to just beyond the left subclavian artery. Proximal rupture into the pericardium had occurred. This was the immediate cause of death. There was severe generalized atherosclerosis with involvement of all three coronary arteries. Microscopic section of the aneurysm wall showed transmural necrosis with acute inflammatory exudate. Atheromatous debris was imbedded in the exudate. No growth was obtained from postmortem cultures.

Discussion

Most clostridial infections are secondary to trauma. Less commonly they are nontraumatic or spontaneous with a reported association with malignancy. Carcinoma of the colon is most frequently reported.[1-3,5]

In a review of *C septicum* bacteremia Koransky et al[3] found a malignancy in 71% of patients, with half being hematologic and half solid tumors. Of the solid tumors, 67% were colon carcinomas. An unusual pattern of spontaneous clostridial infection is the presence of myonecrosis at a site distant from the solid tumor. It is believed that ulcerative lesions of the gastrointestinal tract, especially colon carcinoma, allow clostridial organisms to enter the bloodstream and "metastasize" to the involved muscle.[4,5] Various host conditions, such as diabetes mellitus, atherosclerosis, and immunologic deficiency secondary to cancer chemotherapy, are believed to predispose patients to such infections.[4] It is believed that the metabolic and immunologic changes associated with cachexia and neoplasia create a local tissue environment susceptible to anaerobic infection. Diabetic patients with vascular disease and with a tendency to acidosis are similarly prone to these infections. Although the prognosis of nontraumatic clostridial myonecrosis is poor, early recognition and treatment may be curative.

Mycotic aneurysms develop in many ways.[6,8] Septic embolization from valvular vegetations of bacterial endocarditis can occlude smaller vessels and initiate infection in the vessel wall with destruction and aneurysm formation. In large vessels, it has been theorized that septic emboli may spread through the vasa vasorum and infect the arterial wall.[6] In septicemias, bacteria may lodge in atherosclerotic intimal lesions and aneurysm formation may follow. Similarly, infection of existing aneurysms may occur. Contiguous spread from a localized infection (abscess, cellulitis) to adjoining arteries may result in mycotic aneurysm formation. As a result of trauma or vascular surgical procedures, an arterial wall may become contaminated and subsequently form an infected pseudoaneurysm. A significant number of mycotic aneurysms, however, have no known cause.

The incidence of bacterial endocarditis has declined; currently, most mycotic aneurysms are infected pseudoaneurysms or primary mycotic aneurysms.[8] The latter has been defined as arising in the absence of an intravascular focus of infection and absence of infection in the surrounding tissue. In Bennett's review of 19 cases of primary mycotic aneurysms reported between 1941–1966,[6] the focus of infection was not identified in 42% (eight cases). These have been referred to as cryptogenic mycotic aneurysms by Blum and Keefer.[7] It is believed that these aneurysms originate by circulating bacteria that become implanted on an area of diseased intima.

A review of the literature has yielded only one other case similar to ours. Halevy et al[9] described a patient in whom a mycotic aneursym of the aortic arch developed as a complication of septicemia due to *Klebsiella pneumonitis*. No reported cases of *C septicum* mycotic aneurysms have been found.

Although post-mortem cultures were negative in our patient, the rapid development of the aneurysm and presence of acute inflammation on histologic evaluation is likely due to clostridial infection. In retrospect, the mediastinal air present on the initial chest radiogram represented clostridial infection. Positive blood cultures, obtained once antibiotic therapy was discontinued, likely originated from the aneursym and not the colon carcinoma.

The presence of a spontaneous clostridial infection should arouse suspicion of an occult malignancy, especially carcinoma of the colon.

Bacteremia in patients with severe atherosclerosis should alert the clinician to the possible development of a mycotic aneurysm. Appropriate antibiotic therapy may not prevent its development. Early recognition of these entities may result in successful treatment, although a high fatality rate may be expected in these patients with multiple organ systems disease.

Acknowledgment. We express our appreciation to James B. Turchik, MD, Department of Medicine, Infectious Disease Section, Upstate Medical Center, for help in management of this patient.

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Cerebral abscess in hereditary hemorrhagic telangiectasia

SILVIO D. PITLIK, MD, RAJINDER CHITKARA, MD, MAHMOOD TAFRESHI, MD, JOSÉ A. GIRÓN, MD

Intracranial abscess is essentially a complication of extracranial disease. Since early diagnosis results in a more favorable prognosis, efforts should be directed to detect predisposing conditions such as chronic suppuration in adjacent bone, intracardiac shunt and distant suppurative foci.[1]

In 1951, Hedinger et al[2] described a patient with hereditary hemorrhagic telangiectasia in whom a brain abscess developed. At autopsy the diagnosis of hereditary hemorrhagic telangiectasia was confirmed, and pulmonary arteriovenous fistulas were found.

Hereditary hemorrhagic telangiectasia is a genetic disease with equal sexual penetrance and an autosomal dominant inheritance pattern. The disease manifests with multiple dilatations of capillaries and arterioles, lined by a layer of endothelium. The telangiectases are found in mucosal surfaces of nose, mouth, gastrointestinal tract and kidney. Episodic mucosal hemorrhages typically occur. Arteriovenous malformations are a common feature.[3,4]

We describe a patient with hereditary hemorrhagic telangiectasia who subsequently had a brain abscess, was successfully treated with drainage and antibiotics, and was followed by serial CT scans. We review the reported cases and discuss the clinical, radiologic and bacteriologic findings as well as the therapy and outcome of these patients.[2,5-27]

CASE REPORT

A 27-year-old woman was admitted to Queens Hospital Center on September 8, 1981, with headache of three weeks' duration.

Past medical history was noteworthy for several episodes of epistaxis since childhood. In 1973, at age 19, she had a normal delivery at Queens Hospital Center. At age 21, while in her second trimester of pregnancy, she began to complain of increasing exertional dyspnea and started to suffer episodes of hemoptysis. One day prior to delivery she had new pleuritic chest pain and hemoptysis. Examination showed cyanosis and telangiectases in the fingertips, soft palate, tongue and buccal mucosa as well as finger clubbing. Pulmonary angiography performed after recovery revealed multiple arteriovenous fistulas in both lungs with a right to left shunt of approximately 50%. A diagnosis of hereditary hemorrhagic telangiectasia with pulmonary arteriovenous fistulas was made.

In mid-August 1981, she was admitted for frontal headache. She was given oral dicloxacillin but left the hospital after four days. At home, the headache intensified and radiated to the neck and occipital area. Four days prior to admission, she experienced fever and vomiting.

On physical examination, the pulse rate was 80/min and regular, blood pressure 100/70 mm Hg, temperature 97.7°F, and respirations 24/min. The patient was conscious but mildly lethargic. The neck was supple. Auscultation revealed bruits over both infrascapular areas, an accentuated pulmonic sound and a short midsystolic murmur (grade 1/6). She displayed a depressed affect and bilateral hyperflexia with ankle clonus. Funduscopic examination disclosed no abnormalities.

Electrocardiogram showed sinus tachycardia. Hematocrit was 34%, hemoglobin 10.5 g/dL, white blood cell count 13,800/mm^3 with 85% polymorphonuclear leukocytes, 13% lymphocytes, 2% monocytes. Platelet count was 320,000/mm^3. Serum electrolytes, chemistry profile and urinalysis were within normal limits. Arterial blood gases on room air showed a pH of 7.42, PCO_2 35 mm Hg, PO_2 54 mm Hg and oxygen saturation of 75%. Lumbar puncture yielded clear fluid with a white blood cell count of 395/mm^3 (95% monocytes), a red blood cell count of 360/mm^3, glucose 43 mm/dL, and protein 360 mg/dL. Gram stain and India ink preparation failed to show an organism. Cerebrospinal fluid, blood and urine cultures were negative.

On the day of admission, the patient's temperature rose to 103°F, her lethargy increased and she received 5 million U of penicillin intravenously every four hours, and 1 g of chloramphenicol intravenously every six hours for presumed bacterial meningitis (Fig 1). On the second hospital day, the diagnosis of brain abscess was made and confirmed by isotopic brain scan. CT scan delineated a large, irregular, multilocular isodense lesion (5 by 3.5 cm) with moderate peripheral contrast enhancement located in the left frontal lobe and extending from the base of the brain to the level of the bodies of the lateral ventricles (Fig 2). The left lateral ventricle showed marked compression, and the midline structures were displaced 1.5 cm to the right.

On the fourth hospital day, burr-hole drainage of the left frontal lobe produced about 60 cc of pus. A Scott cannula was left in place. Gram stain of the pus showed abundant polymorphonuclear leukocytes, gram-positive cocci in chains and gram-negative rods. Anaerobic cultures grew *Streptococcus intermedius* and *Fusobacterium* species.

After the operation, the patient became more alert and her headache subsided gradually over five days. She was given phenytoin sodium, 300 mg/day, after surgery and a three-week course of dexamethasone (Fig 1). After 28 days of antibiotic therapy, she had fever with temperatures to 102°F and eosinophilia of 16%. Nine days later a macular pruritic rash appeared. No other symptoms occurred and, nine days after the onset of rash, penicillin therapy was stopped. The administration of chloramphenicol was stopped three days later, but the rash and eosinophilia persisted and only disappeared when phenytoin sodium was discontinued.

On the 55th hospital day, the patient's headache recurred and her temperature rose to 101°F. Surgical aspiration did not produce pus (Fig 1). The patient was then given metronidazole, 750 mg orally three times a day, for 30 days. CT scans obtained at 26, 37, and 120 days after the initial CT scan showed progressive diminution of the frontal lesion (Fig 2). At the time of follow-up, six months after the episode of brain abscess, she was doing well.

DISCUSSION

This patient presented with a rare complication of hereditary hemorrhagic telangiectasia (HHT), previously reported in 29 other patients (Table IA,B).[2,5-27] In this patient, the diagnosis of HHT was known; in 11 previously described patients the diagnosis of HHT was made simultaneously with or after

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From the Divisions of Infectious Diseases (Dr Pitlik, Girón) and Pulmonary Medicine (Dr Chitkara) and the Department of Radiology (Dr Tafreshi), Queens Hospital Center Affiliation of Long Island Jewish-Hillside Medical Center, Jamaica, NY.

Address correspondence to Dr Girón, Physician-in-Charge, Division of Infectious Diseases, Queens Hospital Center Affiliation of the Long Island Jewish-Hillside Medical Center, 82-68 164th Street, Jamaica, NY 11432.

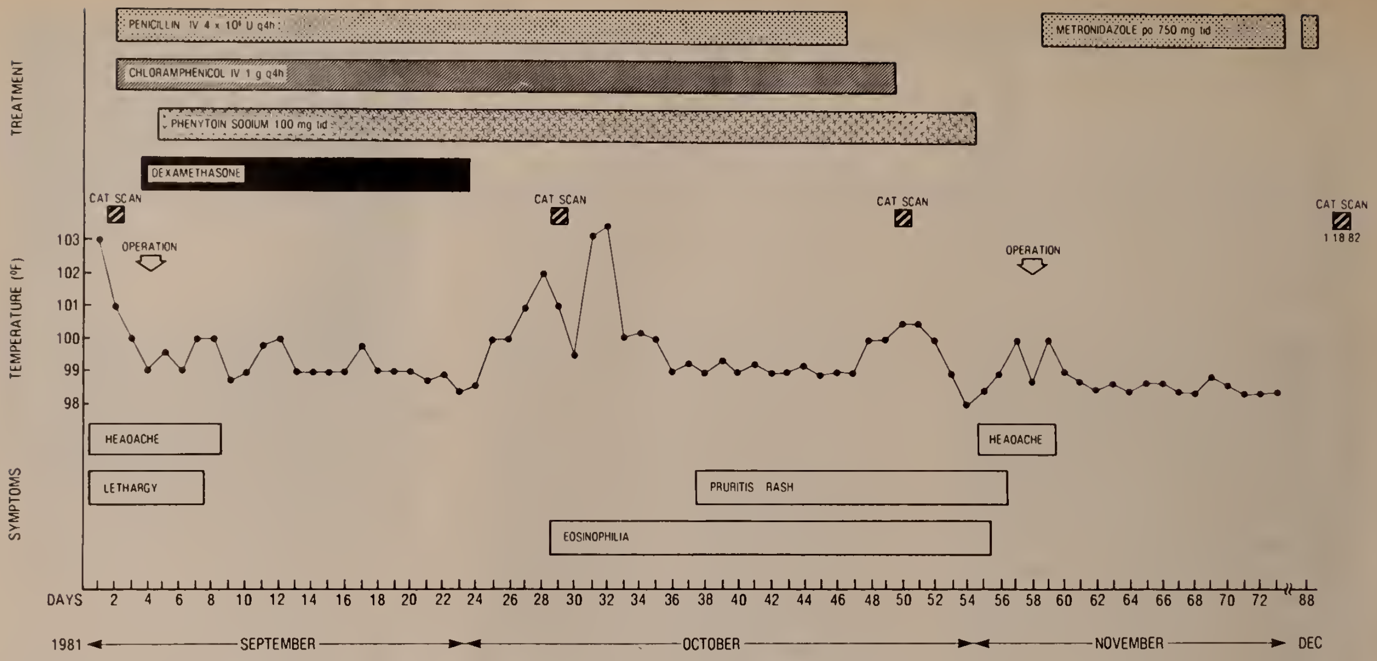

FIGURE 1. Clinical course of the patient with brain abscess and hereditary hemorrhagic telangiectasia.

the episode of brain abscess (Table IA,B).

The most common presenting complaint was headache (15 patients). Headache was localized in only four of the 15, and diffuse in the others. A subacute onset of headache with progressive increase of pain over days to weeks was typical.[2,5-27] Other presenting symptoms were seizures (nine patients), fever (seven patients), mental status changes (seven patients), hemiparesis (five patients), vomiting (four patients) and visual disturbances (one patient).

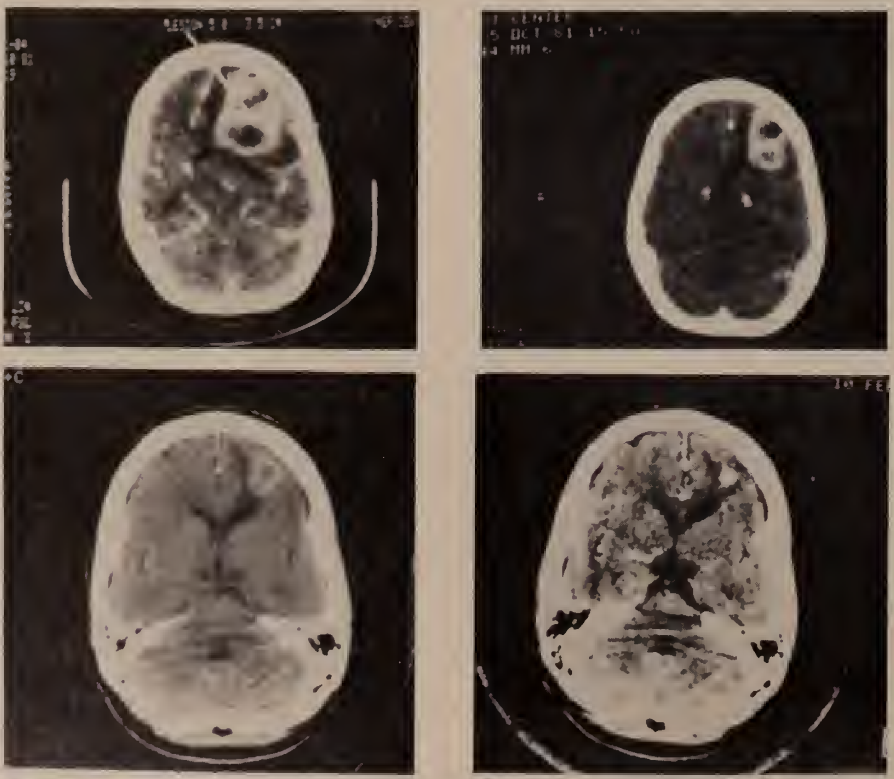

FIGURE 2. Several CAT scans of the head showing initial abscess (upper left) and resolution of the abscess with therapy.

Results of lumbar puncture, reported in seven patients, showed at least one abnormal cerebrospinal fluid finding. Only one patient had a positive culture with *S pneumoniae.* Cultures of the abscess material, reported in 19 patients, revealed a large variety of organisms, predominantly anaerobes (Table IB). The source of abscess material was an operative specimen in 14 patients, and autopsy specimens in five. In 10 patients, a single pathogen was isolated; and in two patients, gram stains were positive and cultures negative; one of these latter patients had foul-smelling pus.

Only five reports, including ours, specified the antibiotics used. Surgical procedures performed on 11 patients included craniotomy with drainage on excision, burr hole drainage, and drainage during ventriculography (Table IB). Two patients had recurrent brain abscesses. Surgical intervention affected outcome. Sixteen of 19 patients who were operated upon, survived; only two of 10 patients who were not operated upon survived. Associated extracranial infections were described in three patients (Table IB). Management of the patients included surgery or antimicrobial therapy (Table IB) or both. Prolonged follow-up is warranted; brain abscess recurred in two of 30 patients.

Findings consistent with pulmonary arteriovenous fistulas, shown by chest film, pulmonary angiography, surgical exploration or autopsy, were noted in 25 of 30 patients. Pulmonary fistula resection was undertaken in eight patients, with satisfactory results.[7,10-12,16,23,26,27] Because of multiple vascular lesions in our patient, this approach was not feasible.

The exact mechanism for brain abscess formation in patients with hereditary hemorrhagic telangiectasia remains unknown. The association of pulmonary arteriovenous fistulas in 20 of the 30 patients reported on suggests a probable mechanism. Meacham et al[13] hypothesized that septic emboli, which bypass the pulmonary capillary bed and infarct brain tissue, set the stage for abscess formation. Alternatively, bland emboli bypassing the pulmonary capillary bed may infarct brain tissue that is then secondarily infected by a transient bacteremia. Transient bacteremias occur after minimal mucosal surface trauma[28] as well as in clinically documented infections. Carter proposed that mucosal telangiectases served as portals of entry for bacteria.[6] Infection of an arteriovenous fistula with secondary spread to the brain may be the sequence of events in some. We did not find a report of a primary infection of a pulmonary arteriovenous fistula. Polycythemia, with its resultant hypercoagulability and potential for cerebral thrombosis,[13-17] is presumed implicated in the initiation of brain abscess. Four of 19 patients in this series demonstrated polycythemia. Imperfect oxygenation with subsequent cerebral hypoxia and increased susceptibility to infarction may also predispose to abscess formation.[13-17] In this series, oxygen saturation was less than 90% in seven of 11 patients. Finally, in patients with hereditary hemorrhagic telangiectasia, either telangiectases or arteriovenous malformations may develop within the brain substance, which may later become infected. Aronson[19] and Roman[25] each described one patient in whom a brain abscess developed in the vicinity of a cerebral arteriovenous malformation. The well-known appearance of telangiectases and pulmonary fistulas with increasing age may be related to this age-related incidence of brain abscess.[14]

Previous infection of ears, sinuses, dental structures or lung, and anatomic disruption from trauma or surgery are presumed to be the sources in most patients with brain abscess.[31] In the group of patients with hereditary hemorrhagic telangiectasia, by contrast, an associated infection at a distant site was found in only three of 30 patients (Table IB). The absence of a primary focus of infection was also noted in the patients with congenital heart disease.[29,30] Thus, if congenital heart disease is excluded in a patient with brain abscess without an obvious primary focus, a search for pulmonary arteriovenous fistulas or hereditary hemorrhagic telangiectasia might be warranted.

In our patient, the CT scan allowed us to follow the resolution of the brain abscess with therapy. Lumbar puncture yielded a bacteriologic diagnosis only in one of seven patients. The cerebrospinal

TABLE IA. Relevant Clinical Radiologic and Bacteriologic Features in 30 Patients with Hereditary Hemorrhagic Telangiectasia (HHT) Complicated by Brain Abscess (BA)

Case No.	Source (First Author)	Year	Age (yr) and Sex	Time from DX of HHT or PAF to DX of BA	Time from DX of BA to DX of HHT or PAF	Clinical Presentation (Chief Complaint)
1	Hedinger[2]	1951	46,M	Years	—	Hemiparesis
2	Kushlan[5]	1952	50,F	—	5 years	NS
3	Bean (CPC)[6]	1953	27,M	10 years	—	Seizures, headache
4	Stern[7]	1953	26,M	—	Simultaneous	Seizures, hemiparesis
5	Stern[7]	1953	43,M	—	Simultaneous	Seizures, headache, aphasia
6	Weiss[8]	1954	27,M	2 years	—	Seizures, hemiplegia
7	Steinberg[9]	1955	39,F	Years	—	Seizures, aphasia
8	O'Neill[10]	1956	22,F	NS	NS	NS
9	Taber[11]	1956	27,M	Years	—	Seizures
10	Syrop[12]	1957	33,M	—	2 years	Seizures
11	Meacham[13]	1958	11,M	—	Simultaneous	Headaches
12	Hodgson[14]	1959	44,M	NS	NS	NS
13	Smith[15]	1963	43,F	—	6 years	Headache, personality changes
14	Latour[16]	1956	26,F	—	Simultaneous	Headache, aphasia, seizures
15	Dyer[17]	1967	27,M	13 years	—	Hypesthesia, headache
16	Dyer[17]	1967	50,M	19 years	—	Headache, mental changes, fever
17	Arnould[18]	1968	52,M	8 years	—	Meningeal signs
18	Aronson[19]	1972	55,M	5 months	—	Mental changes
19	Tyler[20]	1973	14,F	6 years	—	Headache, hemiparesis
20	Tyler[20]	1973	59,F	—	1 month	Headache, fever, stupor
21	Tyler[20]	1973	53,M	Years	—	Fainting, hemiparesis
22	Dines[21]	1974	NS	NS	NS	NS
23	Thomas[22]	1975	NS,F	NS	NS	NS
24	Adams[23]	1977	35,M	1 year	—	Seizure
25	Adams[23]	1977	29,M	5 years	—	Headache, fever, vomiting, confusion
26	Thompson[24]	1977	48,F	—	Simultaneous	Headache, lethargy, visual disturbances
27	Roman[25]	1978	72,F	20 years	—	Nausea, vomiting, headache, fever
28	Errasti[26]	1980	19,M	—	Simultaneous	Headache, fever, nausea, vomiting
29	Harkonen[27]	1981	21,M	—	1 year	Headache, fever
30	Pitlik	1982	27,F	5 years	—	Headache, fever

Abbreviations: NS, not stated; BA, brain abscess; HHT, hereditary hemorrhagic telangiectasia; PAF, pulmonary arteriovenous fistulas.

TABLE IB. Relevant Clinical Radiologic and Bacteriologic Features in 30 Patients with Hereditary Hemorrhagic Telangiectasia Complicated by Brain Abscess

Case No.	Location of BA	Microorganism	Operation	Antibiotic Therapy	Outcome	Follow-Up Period
1	Bilateral	NS	No	NS	Died	—
2*	L. multiple	NS	NS	NS	Cured	5 years
3*	NS	Anaer *Strep*, α-*Strep*, *Actinomyces*	NS	NS	Died	—
4	L. parietal	*Strep*, Anaer GNR	Aspiration	Penicillin, streptomycin, sulfadiazine	Cured	1 year
5	L. temporal	*Actinomyces bovis*	Excision	Penicillin, sulfonamides	Cured	6 months
6	Right	Neg culture	No	NS	Died	—
7	L. parietal	NS	Yes	NS	Cured	4 years
8	R. frontoparietal	NS	No	NS	Died	—
9	R. frontal	*Actinomyces*, GPC	Excision	NS	Died	—
10	R. parietal	NS	Excision	NS	Cured	3 years
11	R. frontal	*Bacteroides*	Excision	PCN, sulfonamides	Cured	2 years
12	NS	NS	NS	NS	Died	—
13	R. temporal	NS	Excision	NS	Cured	17 years
14	L. frontal	*Colibacilli*	Excision	NS	Cured	2 months
15	R. frontoparietal	*Strep*	Excision	NS	Cured	6 months
16	L. temporoparietal	GPC (smear)	Aspiration	Yes†	Cured	—
17	Bilateral	NS	No	Yes†	Died	—
18	L. frontal	*Klebsiella*, *Enterobacter*	No	NS	Died	—
19	R. frontotemporal	Anaer *Strep*, *Bacteroides*	Aspiration	NS	Cured	2 years
20	Multiple	*S. pneumoniae*	No	Yes†	Died	—
21	Frontoparietal	*Strep*	Aspiration	NS	Cured	—
22	NS	NS	NS	NS	NS	—
23	L. temporal	NS	Aspiration	NS	Cured	Yes
24	R. parietal	*Strep*	Aspiration	NS	Died	—
25	L. frontal	*Peptostrep*, *Hemophilus aphrophilus*	Aspiration	NS	Cured	2 months
26	R. Occipital	*Strep*, *viridans*	Aspiration	Yes†	Cured	—
27	Cerebellum	*Nocardia*, GPC (smear)	No	Chloramphenicol	Died	—
28	L. frontal	*Hemophilus* sp.	Yes	NS	Cured	Yes
29	R. temporal	α-*Strep*, enterococci	Yes	NS	Cured	1 year
30	L. frontal	*Strep intermedius* *Fusobacterium*	Aspiration	PCN, chloramphenicol, metronidazole	Cured	6 months

Abbreviations: GNR, gram negative rods; GPC, gram positive cocci; PCN, penicillin. * - other infection found simultaneously with brain abscess (chronic osteomyelitis, one; actinomyces isolated from lung, one; lung abscess, one). † = antibiotics given but not specified.

fluid findings were consistent with an inflammatory process in the brain substance but did not directly point toward a diagnosis.

Therapy of brain abscess in the patient with hereditary hemorrhagic telangiectasia appears optimal when a combined surgical and medical approach is used. Unfortunately, specific antibiotic therapy was often not stated. The anaerobe predominance in brain abscess cultures dictates the use of antibiotics with adequate anaerobic coverage and penetration into the brain. The isolation of aerobes such as *Klebsiella*, *Pneumococcus*, *Colibacilli* and *Nocardia* supports the addition of broad-spectrum coverage for initial therapy until the results of abscess cultures are known. Combination therapy with penicillin and chloramphenicol or penicillin and metronidazole is an adequate initial regimen for these patients.

In conclusion, the symptom complex of headache, seizures, mental status changes, fever, and new focal neurologic deficit in a patient with hereditary hemorrhagic telangiectasia should raise the possibility of brain abscess. These patients usually have one or more pulmonary arteriovenous fistulas. Other neurologic syndromes associated with hereditary hemorrhagic telangiectasia should be included in the differential diagnosis. Conversely, patients with brain abscess of undetermined origin should be evaluated for pulmonary arteriovenous fistulas or hereditary hemorrhagic telangiectasia or both. The incidence of hereditary hemorrhagic telangiectasia in the general population is estimated at one per 100,000,[9] and from 15% to 20% of these patients are thought to have pulmonary arteriovenous fistulas.[14] As shown in this review, such patients constitute a high risk group for brain abscess formation.

Acknowledgments. We acknowledge the cooperation of the Queens Hospital Center departments of radiology and laboratories, the pulmonary service and the hospital library. Dr Fred Rosner read the manuscript and offered helpful comments. Mr Gil Lachow performed a valuable literature search. Ms Barbara Poskrop typed the manuscript through its various phases. Their cooperation is gratefully acknowledged.

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Malignant giant cell tumor of the frontal bone

MIGUEL HERIZE, MD, JACK M. FEIN, MD

Malignant giant cell tumors of the cranium occur less frequently than their benign counterparts and have previously been described at the base of the skull.[1] The occurrence of a malignant giant cell tumor of the calvarium and its elimination by craniotomy may be unique and prompted this report. In contrast to lesions occurring at the base of the skull, definitive surgical treatment of a malignant giant cell tumor of the calvarium may be curative.

CASE REPORT

A 25-year-old woman was admitted to the University Hospital in Caracas in June 1978 because of a rapidly growing painful mass over the right frontal area over a two-week period. The patient first noticed this mass after minor head trauma. Following this incident she described a doubling of the size of the mass. On examination there was swelling, tenderness and hyperpigmentation of the skin surrounding the right frontal mass that measured approximately 8 × 6 cm. Findings on general and neurologic examination were within normal limits. A complete blood count disclosed a slight plasmacytosis (2%) and eosinophilia (11%). Skull roentgenograms (Fig 1) showed localized destruction of both the inner and outer tables of the frontal bone. Carotid angiography showed a vascularized mass supplied by the external carotid artery. There were no significant changes within the internal carotid artery distribution and no evidence of compression of the cerebral hemisphere. Results of a gamma camera study were within normal limits.

Biopsy of the mass was performed on June 22, 1978. Pathologic examination (Fig 2) demonstrated a well-vascularized tumor, whose stroma consisted of fusiform and ovoid-shaped cells with irregular distribution. Mitotic figures were frequent. A dense collection of multinucleated giant cells were observed. There were hemorrhagic and cystic components to the tumor mass. A diagnosis of malignant giant cell tumor was made, but the patient initially declined a complete excision. She was given 4,500 rads of multiportal Cobalt radiotherapy. A craniotomy was performed in August 1978, and the tumor as well as a wide margin of normal bone were removed (Fig 3). The underlying dura was free of tumor. Blood loss was minimal, and cranioplasty was performed. Follow-up evaluation four years after surgery showed that the patient was asymptomatic, and radiographic examination disclosed no evidence of tumor recurrence.

DISCUSSION

The rarity of giant cell tumors of the skull may be appreciated from the fact that less than 2.5% of all primary bone tumors[2,3] are located in the skull, and only 3.5% of all bone tumors are of the giant cell type.[4] Approximately 97% of

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From the Department of Neurosurgery (Dr Herize), Centro Medico San Bernardino, Caracas, Venezuela, and the Department of Neurosurgery (Dr Fein), Albert Einstein College of Medicine, Bronx, New York.

Address correspondence to Dr Fein, Associate Professor of Neurosurgery, Department of Neurosurgery, Albert Einstein College of Medicine, 1300 Morris Park Avenue, Bronx, NY 10461.

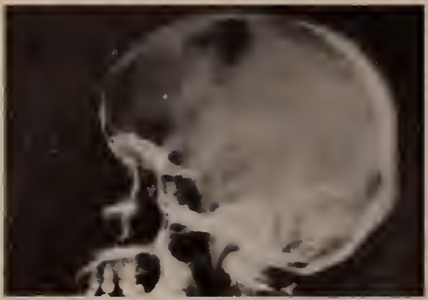

FIGURE 1. Plain skull roentgenogram (lateral view). Irregularly shaped lytic lesion of frontal bone. There is destruction of both inner and outer tables.

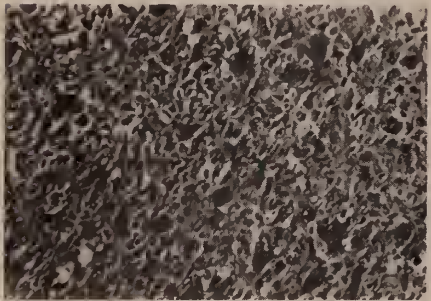

FIGURE 2. Light microscopic section from surgical biopsy sample. Hematoxylin and eosin stain (× 200). Cellular tumor composed of an ovoid-shaped cell with mitotic figures. Multinucleated giant cells are frequent forming one of the more common cell types.

giant cell tumors occur in the long bones, sacrum and patella.[1,4] Jaffe[4] described a grading system (grades 1, 2, 3) based on mitotic activity in the stroma, recognizing, however, that there is no simple correlation between the appearance of mitoses and its biological behavior. Many grade 1 tumors have recurred following curettage, and several grade 3 tumors have been eliminated by excision. Metastases to lung do occur, and the secondary tumor maintains the histologic features of the primary tumor. Once this occurs the average survival time is 10 months.[5] Malignant changes in benign giant cell tumors take on the character of fibrosarcoma and rarely osteogenic sarcoma.[3,6] Invasion of blood vessels has also been documented.[4]

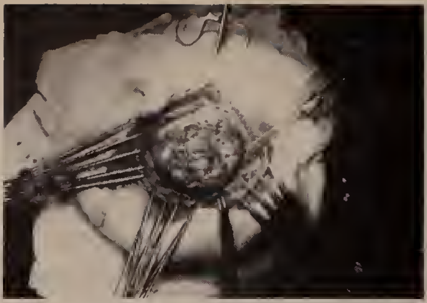

FIGURE 3. Intraoperative photograph showing extent of tumor protruding from frontal bone. The tumor was removed en bloc along with a wide margin of normal bone.

The cranial bones may be involved either at the base[2,7,8] or in the calvarium.[2,9-11] When the base of the skull is involved, neurologic complaints are usually present. The most common location for both benign and malignant giant cell tumors of the skull is in the sphenoid bone. In this location headache and visual symptoms are frequent complaints. Diplopia, disturbances of visual acuity, and proptosis are frequently found on examination. Objective evidence of endocrinopathy is rare. In 12 of 18 cases the patients experienced diplopia, 11 patients had third nerve paresis, seven had visual disturbances, four had proptosis, seven had drooping of the upper eyelid, eight had sixth nerve paresis, two[6,12] showed hypopituitarism, and a pituitary tumor was ruled out. In seven cases the tumor occurred in the temporal bone. Deafness was present in those cases in which clinical data are available. Tinnitus and cranial nerve involvement[7] were found in one case.

Involvement of the calvarium is less common, and involvement of the frontal bone has only been reported in four cases.[2,9,11] Aside from headaches, there were no specific neurologic findings in these four cases. All of the frontal lesions were benign. Keegan et al[11] described a 13-year-old boy in whom the tumor was completely removed. Arseni[9] collected four cases of giant cell tumor in the calvarium. In two of these the tumors were situated in the frontoparietal area; in all four cases the tumors were benign. In one of the three tumors involving the occipital bone,[13] signs of increased intracranial pressure were present.[2]

Because of the unpredictable behavior of this tumor, total excision is the treatment of choice. However, previous neurosurgical experience with malignant giant cell tumors of the skull has not been very rewarding. In those instances, complete excision of a tumor at the base of the skull was not practicable.[1,7,14] In the present case, the calvarial location made this feasible. Radiotherapy and chemotherapy are probably ineffective as primary therapy, and malignant degeneration of benign tumors in association with radiotherapy has been described.[14]

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After 40 years, no signs of decay in fluoride controversy

The decision made by a Long Island community last year to stop fluoridating its water supply, four decades after the first of many studies that demonstrated the efficacy and safety of such treatment in preventing cavities, is testimony to the enduring controversy surrounding this practice.

Ironically, the recent move by Levittown was made just as data from the National Preventive Dentistry Demonstration Program reaffirmed the efficacy and safety of optimal water fluoridation—maximum cavity resistance with minimum discoloration of the teeth. The study included 30,000 children five to 14 years of age in 10 US communities, five with optimal water fluoridation (fluoride concentrations of 0.8 to 1.2 parts per million) and five without fluoridation (less than 0.2 ppm). The study was performed by the American Fund for Dental Health, in cooperation with the Rand Corporation, and funded by The Robert Wood Johnson Foundation.

In a review article on the fluoride debate, Richard J Hastreiter, DDS, MPH points out that the range of fluoridation considered optimal derives from a series of epidemiologic studies done from 1931 to 1942 to determine the relationship between water fluoride concentrations and both discoloration of the teeth and caries formation. These studies were followed by a two-year dental survey of 7,000 school children in 21 US cities (*JADA* 1983; 106:486-490).

Russel B Scobie, MD, a retired pediatrician in Newburgh, NY, has long been an advocate of fluoridation, urging the town to fluoridate its water back in the early 1940s. A subsequent study comparing the prevalence of caries among 4,000 children from 1944 to 1955 demonstrated that the children of Newburgh, which fluoridated its water supply, had 52.2% fewer cavities than their counterparts in neighboring Kingston, which did not fluoridate its water.

Although such findings have not yet ended the controversy, Taimi Carnahan, PhD, a research scientist at the Bureau of Dental Health in Albany, suggested that Levittown's decision is not indicative of a trend in New York. She noted that in 1979, when the state received a federal grant to promote fluoridation of water systems, there were 114 treated systems already on line. These systems served about 68% of the state population that used public water. Since then, 58 more communities have passed resolutions to begin fluoridation. Of these, 37 now fluoridate their water, bringing to about 70% the proportion of the state's population that receive fluoridated public water.

SQUARING OFF IN NEW YORK CITY

The issue arose again late in 1983, this time in New York City, where the health committee of the New York City Council held three public hearings, during which speakers on both sides of the issue presented data on the merits or dangers of fluoridation. According to Charles Epstein, the committee counsel, the resolution to hold the hearings—sponsored by councilman Morton Povman of Queens—stated that the hearings would address "the health dangers posed by the fluoridation of the city's drinking water." When asked if the phrasing of that statement indicated a supposition that fluoridation does in fact pose a threat to health, Mr Epstein told the *Journal* that it was an unfortunate choice of words, and that no such meaning was intended.

At the hearings, Erwin Mandel, DDS, of Columbia University, and Paul Rebich, DDS, director of the Bureau of Dental Health, were among those who testified in favor of fluoridation. Speaking against it were Paul Stephen Beeber, president and general counsel of the New York State Coalition Opposed to Fluoridation, John Yiamouyiannis, PhD, president and executive director of Health Action, and several physicians and dentists. Dr Yiamouyiannis describes Health Action as a tax-exempt organization supported by patrons and dedicated to improving health through the dissemination of information on preventive medicine, health care, physical fitness, nutrition, and environmental health factors. Until 1981, he was coeditor of *Fluoride*, a quarterly journal issued by the International Society for Fluoride Research.

According to Mr Epstein, an "objective" health professional, whom he declined to name, will look over all material submitted in support of each side during the hearing. The committee hopes to release a report of its findings by the end of April, with recommendations for further action by the city council.

The New York City hearings, held almost 20 years after the introduction of fluoridation and despite claims by many health officials that fluoridation is not harmful to health, demonstrate the nationwide schism between the educated professionals on each side of the issue. Indeed, each side refers to different published studies to support its respective claims. In addition, those opposed to fluoridation point to warnings about the hazards of fluoride in such publications as the *Physician's Desk Reference*, which warns that fluoride preparations should not be administered to patients in areas where the fluoride concentration in water is 0.7 ppm or more.

Both sides have also taken the battle to the lay person by means of popular books. *The Health Robbers*, edited by Stephen Barrett, MD, contains a chapter on the fluoride controversy, presenting evidence for both the safety and efficacy of fluoridation. It also discusses the strategies of those opposed to fluoridation for raising doubts about it in the minds of the public, for neutralizing possible political support, and for using referendums to stop fluoridation or to prevent it from being started. Dr Yiamouyiannis's book, *Fluoride—The*

Aging Factor, includes discussions on the effect of fluoride on bones, enzymes, DNA and the immune system, as well as a chapter accusing experts on the other side of the issue of lying.

In addition to claiming that fluoride is harmful to humans, other opponents of fluoridation suggest that it is not effective in preventing cavities, that it corrodes water pipes, and that it deprives individuals of the freedom of choice by forcing fluoride on them.

Yet not only have most consumer groups and national and international health agencies endorsed fluoridation for its safety, effectiveness and low cost, but the decisions of the US Supreme Court and state supreme courts have also upheld the right of the majority to establish disease control programs that affect the entire population (*JADA* 1983; 106: 486–490). Also, Thomas G Reeves, fluoridation engineer for the Centers for Disease Control in Atlanta, GA, told the *Journal* that claims that fluoridation corrodes water pipes are untrue.

> *"The referendum becomes an emotional political process . . . the group that wins the faith and trust of the voting majority emerges the victor."*

Keeping the Controversy Alive

How, then, have those opposed to fluoridation been able to persuade public officials and voters either to halt the practice or not initiate treatment? John Small, fluoridation information specialist at the National Institute of Dental Research, noted that those opposed to fluoridation "create the kind of information that news organizations find exciting. They convince people that a scientific controversy exists as to the safety and efficacy of fluoridation, when in fact, there is no such controversy." He refuted Mr Beeber's claim that the majority of scientific opinion is against fluoridation. "Every developed country," said Mr Small, "supports fluoridation."

The statements of fluoridation opponents, he observed, appeal to basic human concerns of privacy and the harmful effects of pollution, especially in light of recent disclosures of large chemical dumps polluting water supplies. Depending on the location of the activity of those opposed to fluoridation, he said, their major objections vary. In communities with large populations of elderly people, the issue might be that fluoridation causes bone problems or accelerates aging. In those areas populated by many younger people raising families, the red flag may be that fluoridation causes birth defects and still births.

When asked to comment on the reasons for opposing fluoridation, Mr Beeber told the *Journal* that the issues of involuntary medication and corrosion of pipes are minimal as far as his group is concerned. "From our point of view, in the last 10 years . . . the issue has been health effects. If in 1940 I looked at you and said, 'Don't smoke, it'll hurt you,' you'd look at me and say I'm crazy." Chronic ingestion of fluoride over 30 to 40 years, he said, is going to have an adverse health effect. Mr. Beeber claimed that 1% of the population of the US is intolerant to fluoride at any level, meaning that, in New York City, for example, about 80,000 people are very sensitive to the chemical.

However, according to Dr Carnahan, that has never been shown to be the case. Because of the concern over fluoridation, she said, there have been over 1,000 scientific studies on its health effects, and none of these has indicated that fluoridation is harmful to humans. Reports of sensitivity were studied by the American Academy of Allergy and found to be baseless.

Disputing that statement, Dr Yiamouyiannis claimed that fluoridation is a health hazard, stating that, at 1 ppm, fluoride inhibits a number of enzymes, including those responsible for DNA repair, as well as acetylcholinesterase and ATPase. In addition, he said that fluoride causes tumors in fruit flies at levels of 20 ppm and in hamster cell cultures at levels of 30 ppm (which are about 20 to 30 times, respectively, optimal fluoridation levels).

One claim of Dr Yiamouyiannis's that has provoked rebuttal from the Centers for Disease Control in the form of a "fluoridation memorandum" is that fluoridation may cause AIDS. At 1 ppm, he claimed that there is a 25% increase in the growth rate of tumors injected into mice. Furthermore, he said that fluoride levels of 1 ppm increase the activity of AMP cyclase, which leads to an increase in cAMP levels in phagocytes. That, in turn, decreases the ability of these cells to phagocytize substances. "So the biochemistry is there," he said. "I think we have good enough data to indict fluoride and convict it." There are three times as many AIDS victims in areas served by fluoridated water than in those with untreated water, he adds.

Cathy Backinger, Dental Health Program Specialist at the Centers for Disease Contol told the *Journal* that the fluoridation memorandum was prepared to counter the claim that fluoridation may cause AIDS. The memorandum, published in February, states that there is no scientific evidence that AIDS is passed on through the air, food, water, inanimate objects, or by casual contact. It states further that there is no evidence that AIDS is caused by chemicals, such as DDT, dioxin, or fluorides.

It is worth noting the inclusion of DDT and dioxin in that list, especially in light of the critics of those opposed to fluoridation, who say that the opponents tend to latch onto topical health issues.

In response to these health concerns, Ms Colleen Wulf, a county fluoridation consultant in the Division of Dental Health of the Ohio Health Department and 10 other health professionals from around the country have been tracking down the 250 references cited in the anti-flouridationist book, *The Life Savers Guide to Fluoridation*, to determine if the references have been properly cited and interpreted. "It's amazing," she said, "how the scientific literature has been abused."

She noted that some of the references have no relevance to the issue of fluoridation of water systems. As examples, she cited an article on the effect of high levels of fluoride on barley root tips, and another showing in vitro that 32,000 ppm of fluoride disrupts hydrogen bonding—one of the effects cited by some critics of fluoridation as evidence that treated water can harm humans.

A Psychological Basis for Opposition?

The fact that one person's use of the

scientific literature can be another person's abuse is only part of what may keep the perennial fluoridation controversy alive. Another aspect, as pointed out by Dr Carnahan, is that, since fluoridation is one of the few public health measures voted on by the public, "it tends to be a scapegoat for a lot of other concerns." Dr Hastreiter, in reviewing the three major hypotheses developed to explain the persistence of the fluoridation controversy, noted that there may be a psychological component to the activism of those opposed to fluoridation (*JADA* 1983; 106:486-490).

According to the Community Power Structure Hypothesis, "the manner of community decision making defines the ground rules within which fluoridation is considered." The implication of the theory is that the "odds are against the success of a fluoridation referendum, whereas the chance for fluoridation adoption increases significantly as the propensity for centralized decision making is strengthened." Fluoridation, then, stands a better chance if it is implemented as a public health measure by officials than if it is put to a vote.

The Alienation Hypothesis addresses the behavior of the leaders of anti-fluoridation movements stating that, with few exceptions, these leaders possess "true believer psychologic orientations." By selective interpretation of world events and scientific data, they reinforce their commitment.

The Confusion Hypothesis explains public opinion reactions and voting behavior when the issue of fluoridation is brought up for a vote. The major conclusion is that referendum campaigns do not involve the objective presentation of information that voters can use to make a rational choice. Instead, because most voters "do not understand the nuances of epidemiologic analysis, political philosophy and legal precedent around which the fluoridation controversy revolves, the referendum becomes an emotional political process through which the group that wins the faith and trust of the voting majority emerges the victor." Dr Hastreiter concluded that voter support of fluoridation depends upon the leaders that are working for fluoridation displaying a "comprehensive, in-depth command of the issues" and accentuating the positive aspects of fluoridation. A fluoridation referendum debate should be avoided, he suggested, since it usually becomes a forum for those espousing "negative fluoridation allegations and raises the level of voter anxiety and distrust."

On the one hand, then, public health officials are faced with the necessity of getting valid scientific data on fluoridation to the public. On the other hand, they must be cautious of a head-on confrontation, during which opponents of fluoridation may take the liberty of "abusing" the scientific literature in order to win their case.

Today, after 40 years of controversy, about 62% of the US population is served by water systems that are fluoridated. But there is no end in sight to the efforts of opponents. Indeed, when asked if he thought the progress of fluoridation opponents could be described as "good," Dr Yiamouyiannis said, "Good would be showing that everything we said about fluoridation was wrong."

Marc Kusinitz, PhD

Renaissance of the Bernstein Library: new goals, expanded roles

The Medical Society of the State of New York (MSSNY) has opened the resources of its newly enlarged and reorganized Albion O. Bernstein, MD Memorial Library. The library's holdings include 35,000 volumes, comprising approximately 1,300 texts, monographs, and reference works, more than 300 journal titles, many of which date back to the early 19th century, and indices for medial literature from 1880 to the present.

The library first opened in December 1971 with funds from a $100,000 bequest made by the late Morris J. Bernstein of New York City, in honor of his son Albion, a physician who died in 1940 in a traffic accident while on a house call. Although initially established as a socioeconomic research and reference library, its role has expanded over the years to include medicine, basic research, and medical history.

In June 1983 the library's collection was supplemented when MSSNY acquired 25,000 volumes from the Boettinger Library at the Academy of Medicine of the County of Queens. This collection, which had suffered from declining use, was given a renaissance at MSSNY. Mrs Ella Abney, the librarian of the Academy of Medicine of the County of Queens from 1966 until June 1983, took charge of MSSNY's library. In addition to its holdings, the library has access to other medical and law libraries, both through its membership in such cooperative organizations as the Long Island Library Resources Council

Mrs. Ella Abney

(LILRC), or by direct contact with librarians around the state.

Mrs Abney and her assistant, Mrs Eleanor Burns, perform literature searches covering five years of listings in Index Medicus and check facts or verify information on people, places, and issues for MSSNY staff and members. They also provide geneological research on member physicians.

Director of the Division of Scientific Publications at MSSNY, Alan Blum, MD, is both director of the library and editor of the society's journal. The MSSNY library plays a crucial role in the editorial operations of the *Journal*. Dr Blum and the *Journal's* deputy editor, Pascal James Imperato, MD, are able to review manuscripts in greater depth with such ready access to referenced articles and texts. The library also provides background material for articles generated by the staff of the *Journal*.

The main reading room of the Albion O. Bernstein Memorial Library.

Efforts to update and reorganize the library are intended to help it play a major supporting role in the scholarly efforts of physicians. Mrs Abney explains that the library is an important resource for practicing physicians, who are overwhelmed with printed material daily and must leave unread much of what crosses their desks. Such material, stored in a central location by trained personnel, however, is easily accessible when the physician chooses to retrieve the information. Mrs Abney points out that the average hospital library's holdings usually do not exceed 5,000 volumes. Because of their limited space, such libraries cannot hold extensive collections of journals, and much material remains scattered in various departments throughout the hospital. Thus, they must rely on backup collections, such as MSSNY's, in order to respond to the needs of their physicians. The MSSNY library has been playing an important backup role for the Health Sciences Library of Long Island Jewish Hillside Medical Center, for example, since that facility's services became severely restricted following a flood last summer.

Future projects for the library include updating the textbook collection and organizing a file system for news clippings, pamphlets and government reports that will make the enormous fund of information stored on these otherwise "loose" publications accessible. In addition, the introduction of computer capabilities will facilitate literature searches.

MARC KUSINITZ, PHD

FROM THE LIBRARY

FOR MEDICAL LIBRARIES

A medical community with a medical society is invariably progressive, but if it adds to this a good medical library, it adds to its progressiveness stability.

An hospital, a laboratory or a society is often the nucleus of interest about which a medical community gathers, but none of these can appeal so strongly to the largest number of the substantial element of the profession as does a medical library. One of the reasons for this is that a medical library is not possible in a community which is not sufficiently advanced to have a successful medical society. . . .

A society with such a library possesses a great cohesive power. Men who are advanced enough to maintain a society will often rally about the interests of a library when but passive in other things. They may have their differences in the hospital and in the society, but they will be found united for the library. Such a library becomes their pride. They know its worth. Their common interests crystallize about it. It diffuses through the whole society high ideals, a respect for that which is scholarly and worthy of reverence, and a love for the noble traditions of their profession.

As a library develops and grows it should add in the order named the following classes of literature: First, the current periodicals; second, the newer medical books; third, the completed sets of periodicals and reports; and fourth, the older works—the writings of the fathers—in which glimmer the beginnings of the art and science of medicine. Every medical community should have a library begun and developed on these lines.

Editorial
NY State J Med 1908; 8:380

Molecular electronics: organic computers in the 21st century

In the 21st century, carbon-based computers (those with functional components made of carbon chains or rings) may be incorporated into devices as varied as miniature artificial eyes connected to the visual cortex, or robot arms and hands with extremely fine-tuned movements.

The work in this relatively new field, which is called molecular electronics, will be funded in part by the National Science Foundation. Forrest L Carter, PhD, a chemist at the Naval Research Laboratory in Washington, DC, has developed a working definition of molecular electronics: the technology of signal transport and control in nanocomposite structures. (A nano-composite structure is one in which there are active functional components that are or could be different from each other on a nanometer scale. The term "components" refers to sidechains of a carbon-based polymer. These sidechains may differ from each other in length, for example, or as to whether or not they are halogenated. Each sidechain affects the conductive properties of the main chain.)

Researchers now pioneering this field envision large, synthetic organic molecules or genetically engineered enzymes and other proteins that would store and retrieve information. Operating like wires or on-off switches, some large polymers would store information in the binary form of digital computer language (1's and 0's). These organic molecules could act as switches, either by channeling electrons in one direction or by undergoing structural changes that either stop or start the conduction of electrons. Further in the future, enzymes might be used as organic computer chips that would have an important advantage over silicon chips. Since enzymes can exist in more than two conformational states, they are capable of graded responses. Chemical reactions could then convert the graded responses into electrical signals.

In order to make computers smaller and faster, the components controlling the flow of electrons must be reduced in size. The roomful of computers of the 1950s, stuffed with vacuum tubes and metal wires has been replaced by a fingernail-size silicon chip. But whereas the variety of elements (such as transistors) on a silicon chip are measured in micrometers, those made of organic molecules would be measured in nanometers—units a thousand times smaller. It is this thousandfold or so decrease in size that opens the way for carbon-based computers to be implanted inside the human body.

Although there is as yet no carbon-based computer, the conceptual work has been going on for a decade. Arieh Aviram, PhD and Philip Seiden, PhD of International Business Machines (IBM) Yorktown Heights research center, and Mark Ratner, PhD, now at Northwestern University, theorized in 1974 that carbon-based molecules might be used as electric switches (*Chem Phys Let* 1974; 29:274–282). The idea caught the fancy of biologists, chemists, physicists, materials scientists, electrical engineers, and computer scientists. At a workshop on molecular electronic devices last April at the Naval Research Laboratory in Washington, DC, and at the International Conference on Chemically Based Computing held in Santa Monica, CA last October participants succeeded in clarifying some of the short- and long-term goals, as well as the obstacles they must overcome before the carbon-based computer can become a reality.

Any organic compound that is stable in either of two states can be used to manufacture a memory element. Dr Carter has proposed using conducting polymers like *trans*-polyacetylene "wires" for organic computers. This polymer is a zigzag chain of carbon atoms, $(CH)_x$, with alternating single and double carbon-carbon bonds. Following the molecules to the right, for example, might entail moving "up" a double bond (the zig), and "down" a single bond (the zag), or vice versa. Theoretically, when put into an electric field, a perturbation moving along the molecule would cause the positions of the double and single bonds to switch along the length of the polymer. Such a moving perturbation is called a soliton, and its ability to rearrange one stable bonding pattern (single bond-double bond-single bond-double bond, etc) into another stable pattern (double bond-single bond-double bond, etc) could be used as a single memory building unit. A second soliton sweeping down the polymer could rearrange the bonding back to the original pattern.

The soliton is like a moving particle, with its own momentum, its own energy, and its own velocity, according to Dr Forrest. It does not dissipate energy as it moves, so that the energy obtained by converting a double bond into a single bond is used to make a double bond from a subsequent single bond along the chain.

Although the existence of solitons has not been proved, Dr Carter does not doubt the concepts behind this phenomenon. "The theoretical support is quite strong," he says. Dr Carter plans to study single crystals of *trans*-polyacetylene molecules in the near future to test his ideas about solitons.

In order to use this phenomenon to replicate the logic and memory functions built onto silicon computer chips, Dr Carter has suggested incorporating a chromophore, a molecule that rearranges its electronic configuration in response to absorbed light, into the chain. For example, in an olefin molecule, which has a backbone consisting of a pair of double-bonded carbons, absorbed light causes an electron to move from an amine nitrogen at one end of the molecule to oxgen atoms at the other end. The net result is a switch from one electronic configuration ($[CH_3]_2N{-}C{=}C{-}NO_2$) to another configuration ($[CH_3]_2N{=}C{-}C{=}NO_2$). When the olefin is embedded in the polyacetylene chain, it will absorb light only if there is a double bond between the two carbon atoms in the backbone. After a soliton passes along the chain and alters the configuration, there is no longer a path for electron transfer, and the olefin cannot absorb light.

Theoretically, soliton propagation is possible only along a chain of alternating single and double carbon-carbon bonds. Two consecutive single bonds anywhere along the way would block further propagation. Such a limitation can be used to create a three-way soliton valve, with a single carbon atom at the intersection of three long chains. A soliton sweeping down one of the chains would shift single and double bonds around this central carbon atom and block conduction down the other chains by creating a barricade of two consecutive single carbon-carbon bonds at that point in the chain. Each soliton propagated along one of the chains would rotate the three-way valve one stop.

As elegant as this work looks on paper, there may be some major problems. First, no one has proved the existence of solitons. Also, drastic measures, such as liquid helium temperatures might be needed to hold the molecules in the proper conformation for soliton propagation. The chemical structure might also be too fragile to absorb enough light energy to shift bonds in the chromophore. Another consideration is the potential for short circuits as electrons from one switch cross the molecular-width spaces between chains to another switch.

Another molecular electronic device, developed by Richard Potember and his colleagues at the Johns Hopkins University Applied Physics Laboratory in Laurel, MD, is an optically driven switch prepared from thin crystalline films of tetracyanoquinodimethane (TCNQ) complexed with copper. When the film is exposed to a high voltage or to high energy laser light, the film changes from having a high level of electrical resistance to a low level of resistance. Theoretically, such a switch could control the flow of electrons in a carbon-based computer.

> *Until the limitations on digital organic computers are overcome, today's silicon chips will keep a strong hold on the market.*

Until the limitations on digital organic computers are overcome, today's silicon chips will keep a strong hold on the market. Analog organic computers, however, are not burdened with the theoretical and practical limitations inherent in digital computers, which are restricted to processing information according to rigid instructions built into the computer and based upon the strict 1,0 language.

Analog data processing—based on molecular shape—would be accomplished, in theory, by large proteins such as enzymes and cell surface receptors for hormones, that can utilize their three-dimensional structures to store and transfer data. Enzymes, especially, may be suited to the task by virtue of the varied conformations they can assume. This property enables enzymes to respond in a graded, "analog" manner, and makes them especially useful for pattern recognition and fine control of movement of robot arms and hands. Although enzymes work at rather slow speeds (about one ten-thousandth of a second for substrate recognition and catalysis), their ability of pattern recognition is a feat that would take a digital computer much longer to perform. Protein-based computing elements, or, biochips (referring to their biological origin), appear to be quite suited for sensing and control systems that would be integrated into larger, silicon-based computers.

Michael Conrad, PhD, professor of computer science at Wayne State University in Detroit, MI, has suggested one application for biochips. According to his scheme, a robot eye would transform visual input supplied by a television camera into analog electrical signals by means of a series of chemical reactions. The analog signals would, in turn, exert fine control over the robot's functions.

In the first step of Dr Conrad's scheme, the television camera reduces a scene (such as an object the robot is to grasp) into a mosaic of small picture elements called pixels that activate photosensitive chemicals. This activation, with the subsequent creation of a reaction product, would be proportionate to the color and intensity of each pixel.

The chemical product then interacts with the underlying second layer, which is made up of enzymes or surface receptors. By having enzymes or receptors catalyze another reaction on a lower level, the initial reactions could be amplified through a cascade effect that would eventually generate a macroscopic chemical gradient.

Finally, the gradient would be detected by an array of biosensors—hair-thin devices now being developed and tested for use as blood pH or blood glucose concentration measuring instruments that can be inserted into the body. The biosensors would act as transducers, turning chemical gradients into analog electrical signals that would control robot arms or send information in analog form to a receiver that could extract information from the signals, possibly for use in artificial sensing devices or as part of an artificial human eye.

Some of the problems inherent in such a scheme are how to keep the proteins in this biochip functional over long periods of time, how to reset the system after each mosaic of pixels is processed, and how to assure that the response time of such a setup would allow rapid hand-eye coordination. An advantage to this design is that the graded-response nature of the system would tolerate small changes in patterns. A slight change in the shape of the letter G, for example, would result in only a slight change in the analog output signal, and allow the eye to recognize the letter despite the change. This ability to adapt to subtle variations in input would make such a biochip more versatile than a digitally-oriented silicon chip.

The basis for another type of molecular switch dates back many decades. In the 1930's, Irving Langmuir and Katharine Blodgett developed the basic technology for assembling layers of films. They spread molecules having a hydrophobic and a hydrophilic end onto the surface of a water bath. When a glass slide is slid into the water slowly, a single layer of molecules adheres to the slide as it is removed, with the hydrophobic ends oriented away from the slide. Each subsequent immersion and withdrawal from the water adds another single layer. Using this technique, Hans Kuhn of the Max Planck Institute for Biophysical Chemistry in West Germany built up multilayered films containing light absorbing and light-emitting dyes that could be used to make optically driven molecular switches.

The proteins in such devices pose a problem in that they are stable only in water solutions near neutral pH, and at temperatures below 120°F. Since the fragility of natural proteins makes them unreliable and restricts the conditions under which they can be used, genetically engineered proteins may be more

Biochips are "just too far in the future to talk about."

useful according to Kevin M Ulmer, a theorist in the field of biochip design, from Genex Corporation in Gaithersburg, MD.

Biochip proteins would be engineered by either modifying DNA sequences that code for the amino acid moieties, or, ultimately, by synthesizing new genes, perhaps by means of the currently available gene machines, or by cloning isolated strands of DNA. Either way, the DNA would be inserted into bacteria, which would then make millions of these proteins. If synthetic genes coding for proteins that are chemically attracted to each other were assembled in specific ratios before being inserted into bacteria, the artificial proteins produced would assemble spontaneously into functional complexes. Before this can be done, however, much more must be learned about how to predict the three dimensional shapes of proteins from the constituent amino acids.

The idea of using biological organic compounds to process information may suggest such terms as "biological computer." But such a reference is not apt. Natural proteins do not conduct electrons. Also, most computers can manage only one operation at a time (sequential processing), while the brain is capable of parallel processing. Moreover, computers transmit data by means of electron movement, whereas nerve cells transmit data by movement of relatively bulky ions across their membranes and movement of neurotransmitters between neurons.

Biochips are "just too far in the future to talk about," asserts Dr Carter. He points out, however, that the "biological world knows how to self-synthesize and how to self-organize. And we don't know very well how to do it. We ought to spend some effort learning those principles . . . and trying to transplant them to the [non-living] organic world and to the inorganic world."

MARC KUSINITZ, PHD

SUMMER RESEARCH ASSISTANT POSITIONS AT THE *JOURNAL*

Applications are invited from medical students (including those who will be entering medical school in the fall) for the position of research assistant at the *New York State Journal of Medicine*. This 10-week paid position is an opportunity for a student to participate in the editorial process of a peer reviewed scientific journal and to develop an original project for possible publication. Inquiries should be directed to the Editor. Applications should consist of a curriculum vitae and a covering letter. Deadline: May 4.

A second paid position of six weeks duration is available for a student or resident to assist in a project on alcohol problems. Inquiries should be directed to the Editor or to Albert B. Lowenfels, MD, Professor of Surgery, New York Medical College, Valhalla, NY 10595.

The Sick Citadel

By Irving J. Lewis, MA and Cecil G. Sheps, MD. 363 pp. Cambridge, MA, Oelgeschlager, Gunn and Hain, Publishers, Inc., 1983, $25.00.

Social institutions experience cycles of development and decline in response to the forces that give them birth. In little more than two decades, academic medical centers have run a telescoped cycle from preeminence to potential eclipse as shaping forces in our nation's health care system. They grew rapidly in size and influence on the aspirations of the Great Society. Now with the Great Society a distant and deflated dream, they face the realities of economic constraint, deflected social ambition and a sharp shift in national health policy.

Academic medical centers—the administrative combination of a medical school, a university hospital, and health professional schools—are largely American phenomena. They were created in the early 1960s as administrative devices to buffer university presidents from the urgent daily demands of medical school and hospital operations.

They grew in size and influence in the 1960s and 1970s largely because they were ready-made channels for public funds aimed at the expansion and reform of the nation's health care services. They linked education, research and service as no other institution could. They became the logical vehicles for such varied programs as regional and comprehensive health planning, expansion and better distribution of health care personnel, facilities and services, experimental programs in the use of auxiliary personnel, minority recruitment, continuing education, health education and preventive medicine. Indeed, every new program aimed at improving the nation's health or the delivery of health services sooner or later found its locus in the academic medical centers. They became the "citadels," as described by the authors in this interesting book.

Today, that citadel is sick and troubled. A series of new and anticipated forces has eroded its dominant position—rising costs of health care in an unstable economy, a conservative shift in national politics away from governmental roles in social and health care towards competition, cost containment and the growing competition of large community hospitals, and for-profit hospital corporations. Most significant is the sharp shift in public attitudes from health care as a civic right to health care as a commodity to be shopped for and purchased in a competitive marketplace. Regional planning, cooperative networks, and regulation have yielded to market forces, deregulation and anti-trust fervor. And, what is most significant, these changes have occurred without the participation of the academic medical centers, in some cases even in spite of them.

The citadels of yesteryear are in a quandary of value choices that promise to reshape their images in drastic ways. From the beginning the academic medical centers were forced to make some Faustian compacts since their prime social purposes of research and education have never received full or direct funding. In their early years, academic medical centers could accommodate the public interest in health care reform, since there were sufficient funds to support research and education as well as community programs. And, they managed the compromise well. Today, however, support for education and research must come in large part from patient care income, in competition with institutions not burdened with costs of education and research. Academic medical centers have become big business, threatening the quality of their academic enterprise.

It is the complex interaction of these forces during the birth, growth and potential decline of academic medical centers that the authors describe in this important book. The authors are two of the most astute, knowledgeable and experienced participants-observers of the history of academic medical centers. Together they combine an unusual depth and breadth of expert knowledge ranging from the viewpoint of the federal, budgetary and policy making sector to the daily operation of large academic university hospitals and medical centers. A better combination of authors would be hard to find.

They develop two major themes throughout their book. The first is that following World War II public support for academic medical centers was directed at expansion and equitable distribution of health care services rather than research, so that public and faculty interests were not congruent. Recent social and political events, they contend, now make it clear that government can no longer accommodate this dichotomy of academic and public aspirations.

Their second major theme is that the public interest is better served by a closer, but more realistic, alliance between government and academic medical centers. Both are needed to bring "order" into our health care system—the government to supply the funds and framework, the centers the core of experts needed to meet the community's health care needs. The dichotomy is resolved, they suggest, by putting education and research at the service of the community's health rather than the faculty's research interests.

The authors establish their theses in a series of detailed and well-documented chapters tracing the political and historic evolution of academic medical centers, their role in health care delivery, and the expansion of medical research and the production of health care personnel. The expenditures, financing, governing power and educational philosophies of the citadels are all competently and accurately reviewed. The authors conclude that government and academic medical centers are mutually dependent, and that they must enter a new era of productive cooperation based on different terms than in the past.

It is not difficult to agree with the authors' sociohistorical description of the forces acting upon academic medical centers from within and without in the last two decades. It is their recommendations for the way the changing forces should be confronted in the future that I believe is most in doubt. The authors of course realize this, and in their last chapter they set forth their assumptions and recommendations, together with their anticipation of the impediments and objections those recommendations will encounter.

It is on this last chapter, which argues for a specific future role for academic medical centers, that I wish to concentrate my commentary, since I believe the data they present can be interpreted in other ways.

First, let us look at what they call their "continuing assumptions"—namely, that the major determinants of public policy will be—equity of access, competition and cost containment, a physician surplus, continued growth of medical technology and regionalization. They do not establish clearly whether these are central concerns of policy makers or of the American people or their own hopes for what ought to be the case. These distinctions are of the utmost importance in assessing the validity of the authors' claims.

Their most debatable assumption is that equity of access to health care is a genuine concern of policy-makers today. One can agree that this *ought* to be the case; however, there is no evidence that this is in fact so. In the present political and economic climate, policy-makers, and even the general public, have virtually given up the rhetoric of equity. The elevation of cost containment and competition to quasi-ideological status has dampened, and in some places even obliterated, previous concerns for equity. We hear far less talk today about health as a "right," even from liberals. How potent a force is equity in shaping public policy? Certainly it cannot be much of a concern in the for-profit sector, which realistically must concentrate on a return for its investors.

In fact, if we accept the assumption about the continuation of competition for scarce resources, the best we can hope for in public policy is for minimal or baseline health care for those who cannot pay equity. Even these minimal provisions will be difficult to maintain in the event of an economic disaster. We can agree with the authors that competition will be a driving force but not necessarily in the direction they indicate.

The physician surplus is another debatable assumption. The definition of a surplus depends upon the future roles of physicians. There is no question that in some specialties a surplus exists. Already specialty organizations are taking steps to limit access to residency training. However, if equity were to become a national policy again, there might well be a very great shortage of physicians in primary care specialties. Unlike equity of access, the prospect of a physician surplus does have enough credence to lead policy-makers to favor cuts in enrollments in medical and other health professional programs.

The assumption of continued growth of technology is, on the whole, unquestionable. But, there is one caveat. Present policies that limit support for young investigators could inflict serious damage on our future research potential in the medical sciences. Without a continuing supply of basic and clinical investigators, academic health centers would suffer corrosion of one of their social functions. This would be the case too if the authors' recommendations about which investigations to support were followed.

Finally, the authors' hope for rationalization through regionalization is, like the assumption of equity, more a hope than a reality at the moment. There is no sign that decentralization, deregulation or the forces that spawned the new federalism are waning. Nor is there any evidence that states or local communities are enamored of, or capable of, planning at the community level. Moreover, planning, which implies cooperation among providers, is discouraged by the recent Federal Trade Commission rulings and Supreme Court decisions that exhalt competition as a prime value. Providers collaborating in the regionalization of services, prices or plans would face legal challenges.

There is an unavoidable ambivalence about the authors' assumptions. They gloss over the recent sharp shifts in public sentiment and policy. They project aspirations that were common to public policies about academic medical centers a few years ago. Those aspirations do not square with national policy shifts of the last 3 to 4 years. The assumptions therefore are more in the nature of nostalgic hopes about what ought to be the role of academic health centers than realistic assumptions about the forces actually driving health care policies today.

The authors are too experienced not to be fully aware of these ambivalences. They see the problems in the new federalism but nonetheless hope that recognition of social need will ultimately slow the swing of the pendulum. They seem assured that the public's health will eventually require the reforms they envision in academic health centers and in their relationships with government. This is an open question indeed.

The authors have advanced these same reforms in their writings over the years. Academic medical centers must take a role of leadership in meeting the needs of the public, and this calls for a unified effort by both medical school and hospital, each making the health of the community its major focus, not just coincidental. The corollary to this is that the Flexnerian model of research and education as prime goals must give place to a concern for studying and delivering service to a designated community. Only in this way can academic medical centers realize their potentials as natural resources. This, in turn, requires strengthening the powers of medical center executives, as well as medical center budgeting, planning and priority setting; this means limiting the dominant role of the medical school in favor of the medical center administration. The authors contend repeatedly that the Flexnerian model can be transformed into one in which meeting community needs is its prime focus for teaching, research, and service. Taken together, these form their blueprint for "constructive leadership," towards which academic health centers should move.

The impediments to such a set of reforms are formidable, and they are recognized by the authors. Unfortunately they are not dealt with point by point, but will be the focus of criticism by those who do not see the Flexnerian model in such negative terms. This reviewer is of the opinion that some middle ground between the complete submission of the academic health center to the needs of research and education on the one hand and meeting community needs on the other is possible. Rather than risk a continual and enervating tension between service and academic pursuit, or a dilution of one by the other, it is more realistic to recognize the differences between them as fundamental. And, while accepting the importance of each, organize the medical center such that there is a partitioning of functions, and funding between them.

On this view, the medical school would dedicate itself unapologetically to undergraduate medical education, graduate education of basic scientists, and clinical investigators. The university hospital, its clinics and its clinical faculty would dedicate themselves primarily to clinical service, residency training, meeting community needs and playing a major role in modifying the health care system in its community. The former would be financed by tuition, research grants, and university funds and the other by fees for patient health care contracts and public funds for specific services.

The academic medical center would remain as a coordinating entity, linking the education and research with the hospital and patient care enterprise. The academic medical center would be more in the nature of a holding company—facilitating cooperation, planning, communication and partitioning of functions. It would be governed by an interlocking directorate of board members from the university, the hospital board and the patient care enterprise.

In this way, the major elements of the academic medical center could pursue the goals appropriate to each. Funds from patient care would not be combined with those for research, nor would patients carry any of the costs of education. The conflicting pressures on clinical faculty to earn their way on the one hand, and do research and teaching on the other, would be reduced. In addition, academic and research departments would not necessarily overlap, faculty members would advance in rank depending upon which functions they perform, and clinicians and researchers would be judged by different criteria.

Essential to such a partitioning of function is a critical reexamination of what is essential in carrying out the unique social responsibilities that devolve upon academic medical centers. Painful and threatening questions will have to be faced about some of the most fundamental assumptions of both the Flexnerians and the proponents of the Sheps-Lewis view. This is not the place for an examination of the value choices involved. I have sketched my own thoughts in more detail elsewhere.[1]

I believe with the authors that the academic medical center is indeed an important national resource, that its potentialities are yet to be fully realized, that it must respond to the changing complexion of public policy and community need, that the university hospital should be primarily for patient care and that the academic medical center is the only place where teaching-research and community service can be effectively linked. I disagree with their assumptions about what forces will shape public policy in the immediate future, with their subordination of teaching and research entirely to community service. Their "new" model is really an extrapolation of the model favored by many medical educators and public policy makers in the 1970s, although it was never fully realized precisely as sketched in this work.

I believe that the social utility and variability of the academic medical center is best assured by a recognition of its two major functions, by clarifying the differences between them, funding and staffing them differently and balancing their contributions through the academic medical center organizational structure. Difficult as this balance can be to maintain, it is preferable to yielding the primacy to one pole or the other of the research-teaching versus patient care-community service dichotomy.

Leaving aside some redundancy in the socio-historical analysis, as well as a tendency to equate hope with reality, this is a cogent, informed and accurate account of one of the most important social institutions of our times. We are indebted to the authors for their obvious display of knowledge, judgment, and wisdom.

This is clearly the best work of its kind. It is no overstatement to put it into the category of must reading for all health professionals—practitioners and educators alike, for policy makers and legislators, and anyone who thinks, writes about or makes decisions about health and health care in this country.

EDMUND D. PELLEGRINO, MD
Director, Joseph & Rose Kennedy
Institute of Ethics and
John Carroll Professor of
Medicine and Medical Humanities
Georgetown University
Washington, DC 20057

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[1] Pellegrino, ED: *Academic Health Centers and the Medical Marketplace: A Faustian Compact Examined.* Proceedings of the 1982 Annual Meeting of the Association of Academic Health Centers, Kiawah Island, SC Sept 29–Oct 2, 1982. January 1983, pp 19–39.

A HEALTHY STATE: AN INTERNATIONAL PERSPECTIVE ON THE CRISIS IN UNITED STATES MEDICAL CARE

By Victor W. Sidel, MD, and Ruth Sidel, PhD. 398 pp., New York, Pantheon, 1983. $8.95.

To understand the viewpoint of the Sidels towards health and medical care in the US, readers must keep in mind the purposes they attribute to the health-medical care system. Their contention is that the health-medical care system serves four purposes: (1) an increase in equity and justice; (2) a strengthening of individual, family and community competence and well-being; (3) the protection and promotion of health; (4) the organization and provision of humane and technologically appropriate care for the sick and the "worried well." With these purposes in mind, the Sidels have updated the 1977 edition of this book with postscripts at the end of each chapter and additional footnotes.

In addition to reviewing the condition of health-medical care in the US, the Sidels also have separate chapters on the health care systems in Sweden, Great Britain, the Soviet Union and the People's Republic of China. The authors have visited all of these countries on numerous occasions. Thus the facts they present are in large measure derived from first-hand knowledge. In addition, there is an historical chapter on the past and present of health care in the US followed by a chapter with proposals and prospects.

What emerges from all of this is a book intended for the general reader that skillfully blends facts and figures into a readily comprehensible picture of the state of our nation's health. A variety of figures and charts dramatically disclose that the US is not the world's leader in infant survival, longevity, or in providing basic primary care for all. Rather, the US stresses the provision of sophisticated technology for a relative few. Within the US health-medical care system, incentives are awarded for the increased utilization of hospitalization rather than for expanding ambulatory care and/or home health care. Generally speaking, the Sidels decry the current efforts to reduce programs of a public health nature such as immunizations, prenatal care, well-baby clinics and many other long established and proven preventive measures that were instrumental in attacking the high mortality and morbidity problems of the early 1900's.

Much of the fault for the malaise in the US health-medical care system is laid at the foot of Reagan administration policies. As the Sidels see it, health-medical care in America is being channeled into the "corporate" vein of private enterprise and more for the rich. More and more of the "medical-industrial complex" is turning toward "corporatization" wherein the hospitals, the free standing emergency rooms, the home care suppliers, the hospices, and the nursing homes are being sold on the stock exchange and advertised as superior fiscal investments.

In summary, the Sidels note that the potential they saw in 1977 for constructive change in the US health-medical care system has turned to dust, at least for the political moment.

Both Sidels have been able and accurate observers of the health care scene for many years. In fact, Victor Sidel has recently become President-Elect of the American Public Health Association, a nationwide organization concerned with the public's health and well being.

This book is highly recommended for anyone who wishes to be conversant with the issues involved in providing health and medical care to people. Particularly these days, when cost-containment is the watchword, it is illuminating to compare US care with those nations spending less and doing better. Even though the British National Health Service is often criticized in the US, the Sidels feel that we can still learn a great deal about establishing a mechanism for delivering care to all. The book covers issues that can be discussed by students in all types of health-medical education institutions, as well as by students in social work, law, public administration and related fields. Using the Sidels as a source, students would be able to pursue the issues with proposals and suggestions. There is a wealth of information to satisfy the intellectual curiousity of those generally concerned with health-medical care in the US.

However, not everybody will abide by the utopian purposes that the Sidels have set for the health-medical care system. Yet, I would even advise those skeptics to read the book because it is always prudent to learn about the other point of view.

For those who already own the 1977 edition, I can only say that the postscripts do change some of the Sidels' opinions. There is a new government in Sweden, China had a change of leadership and the Soviets and British seem to be undergoing significant health status changes.

All in all, this book should provide a battleground for a serious consideration of exactly what constitutes "a healthy state."

ALLEN D. SPIEGEL, PhD, MPH
State University of New York
Downstate Medical Center
New York, NY 11203

HEALTH AND HEALTH CARE IN NEW YORK CITY: LOCAL, STATE AND NATIONAL PERSPECTIVES

122 pp., New York, United Hospital Fund of New York, 1983. $20.

This book includes an up-to-date and graphic overview of the health status of New Yorkers and their health care delivery system, and provides comparisons with New York State and national data. It is a valuable resource, providing the most recent information on various aspects of health care and health care trends. The book is designed for use as a reference manual for health planning, decision making, and reporting by health administrators, policy makers, students, and anyone involved in delivering and using health care services. As such it is a useful addition to the medical care and community health literature.

The volume has five main divisions, including chapters on demography, health status, hospitals, nursing homes, physicians and health care finances, plus a list of references on current publications on health policy, voluntarism, special studies, health care information series and data resources for New York City.

Chapter I describes the size and characteristics of the population of New York City and its boroughs, New York State, and the United States, by age, race, and number of people receiving public assistance.

Chapter II gives an interesting comparison of the health status of the city, state, and nation by birth and death rates for a period of 40 years. Data on death rates for selected causes, such as infant mortality, influenza, pneumonia, and homicides are given from 1901 to 1980.

Chapter III identifies the latest number and types of hospitals in New York City, New York State, and the nation. It includes their use as estimated by number and percent distribution of beds, admissions, patient days and rates, discharges, length of stay, ambulatory care and emergency department visits.

Chapter IV describes the types of nursing home beds available in New York City, as compared, not only with the state, but also in particular, with New Jersey and Connecticut, and the nation as a whole. It also includes information on office-based physicians and medical education.

Operating deficits, average charges, Medicaid expenditures with type of service identified, are all included in Chapter V. This chapter is very useful for problem solving and decision making in health care financing.

The data contained in this book were gathered from the most reliable sources. The book is attractively assembled with easy to read graphic data, is well organized, and in general, is an excellent reference for both experienced health care providers, and those in other disciplines.

NICETAS H. KUO, MD, MPH
Flushing Hospital and Medical Center
New York, NY 11355

CLINICAL PARASITOLOGY

Ninth Edition. By Paul Chester Beaver, PhD, Rodney Clift Jung, MD, and Eddie Wayne Cupp, PhD. 825 pp., illustrated. Philadelphia, PA, Lea & Febiger, 1984. $51.50.

Parasitology has received increased attention in the United States in the past several years because of increased parasitic disease incidence secondary to changes in life styles, and originating from overseas. Since the last (eighth) edition of *Clinical Parasitology* was published in 1970, much has changed in the epidemiology of many parasitic infections, in available treatments, and in our knowledge of the parasites themselves.

This volume is authored by Paul Chester Beaver, the dean of American parasitologists, Rodney Clifton Jung, a world renowned authority on clinical parasitology, and Eddie Wayne Cupp, a leading expert on medical entomology. They have imparted to it their enormous knowledge of a vast subject, their brilliant scholarship, and their splendid writing abilities, making this book the most comprehensive, definitive and readable volume in the field.

Previous editions of *Clinical Parasitology* were recognized as classics in the field. The present edition upholds that tradition. Retaining much of the best material from the older editions, the authors have added an enormous corpus of information about newly discovered parasites (some 20 in number), new modes of transmission and diagnosis, and the impressive array of newer and safer drugs that have made their appearance in the past several years.

The format of previous editions, of proven success with readers, has been retained. But newer illustrations and updated figures and references replace older ones. Electron micrographs and scintigrams have been used to illustrate appropriate sections. The four chapters of the technical appendix contain up-to-date information on culture methods, immunologic diagnosis, entomologic methods and the routine examination of blood and feces, as well as autopsy, biopsy and environmental materials for parasites.

Various chapters appropriately deal with the problems of sexually transmitted parasitic diseases and parasitic diseases among those with Acquired Immune Deficiency Syndrome (AIDS). The problem of *Plasmodium falciparum* resistance to standard anti-malarials such as chloroquine and amodioquine is discussed in great detail, as are the newer anti-malarials mefloquine and qinghaosu (artemisinine). The latter is the active anti-malarial principle of the Chinese herb, *Artemisia annua* that has recently been field tested with promising results. The five pages that cover anti-malarials and the various clinical situations for their use are thorough and up-to-date. But it is not easy to find the needed clinical situation at a quick glance. A table or two would have made the presentation of this information easier to follow. This, however, is a minor quibble.

The book is enhanced by a 44-page index that includes subject, figure and table information. The author index, a prominent feature of previous editions, has been deleted. The length of the book is 825 pages, compared to 890 pages for the eighth edition. Given all of the new information in this book, this is indeed remarkable. It was achieved in part by using a slightly larger page size, but much editing was also done to eliminate older and less useful information.

Clinical Parasitology is a superb volume, authoritatively authored, comprehensive, complete and easy to read. It is beautifully bound, printed on a coated stock and reasonably priced at only $51. It should be in every medical center and hospital library. Parasitologists, clinical pathologists and public health officials will find it a definitive reference. However, the book's reasonable size, format and extensive authoritative coverage of diagnosis and treatment make it a reference that should also be in the office of every practicing internist, primary care physician, general practitioner and family practitioner.

There are thousands of medical texts published annually in the United States. But few achieve the status of classics. *Clinical Parasitology* is one that does.

PASCAL JAMES IMPERATO, MD
Deputy Editor

DIABETES: A NEW AND COMPLETE GUIDE TO HEALTHIER LIVING FOR PARENTS, CHILDREN AND YOUNG ADULTS WITH INSULIN-DEPENDENT DIABETES

By Lee Ducat, MD and Sherry Suid Cohen, MD. 263 pp. New York, Harper & Row, 1983. $13.95.

This book was written by the founder of the Juvenile Diabetes Foundation to answer questions that insulin dependent diabetes patients and their families may have about its diagnosis, treatment, and complications. The book offers practical information needed to deal intelligently with this disease. It also proports to make the reader aware of the progress that has been made in the management and treatment of diabetes, and is a resource for more effective health care for the diabetic youngster.

The book is divided into four sections according to the age of the individual: Sugar Babies, Sugar Kids, Sugar Teens and Sugar Grownups. Each section can be utilized effectively by parents, children or health professionals concerned with a particular age group. However, the book is best read in its entirety. It is well written, concise and authoritative. Many practical aspects of self-care and care of children with diabetes are presented. The truth is never distorted, although the tone is usually optimistic. The book offers parents many practical suggestions for improving the daily management of the child with diabetes. The patient is also provided with reassurance and a good sense of balance between caution and concern.

I found this an easily readable and knowledgeable discussion of the multiple challenges facing the youngster with diabetes and his or her family. It is reasonably priced and is highly recommended for those with diabetes, and especially for individuals with newly diagnosed diabetes and their families. The final chapter gives physician and clinic resources for patients with diabetes. Although not exhaustive, it lists many of the recognized authorities in the field.

This book can also be read by physicians who will quickly appreciate the multiple concerns of the families of patients with diabetes. It is recommended as an excellent guide that physicians can use with their patients.

I. RONALD SHENKER, MD
Long Island Jewish-Hillside
Medical Center
New Hyde Park, NY 11042

AMERICAN COUPLES: MONEY, WORK, SEX

By Philip Blumstein, PhD and Pepper Schwartz, PhD. 656 pp. New York, William Morrow, 1983. $19.95.

American Couples presents an extensive sociological study that was largely funded by two major foundations. The two authors, Drs Philip Blumstein and Pepper Schwartz, studied four kinds of couples: married, cohabitating (unmarried heterosexual couples) and same sex relationships (both gay and lesbian couples.)

The impetus behind this study is the vast social change that has taken place during the last twenty years. Its impact on both the stability of marriage as an enduring social institution, and the rise of other forms of intimate relationships is examined. Twelve thousand questionnaires representing responses from each partner were received and followed up with selected interviews and further questionnaires. The first chapter offers an historical analysis of the American Couple, providing a framework for introducing the major issues. Here the authors identify essential questions to be addressed regarding permanence, commitment and changing gender roles. Some major questions raised are: Can the institution of marriage survive with the continuing high divorce rate and changing role of women? Will other forms of relationship take precedence? Three major themes are chosen to examine closely the values and behavior of each of the four kinds of couples. They are money, work and sex. These critical themes form the basis of evaluating who has power, how power is exercised, and how power affects relationships. Marriage as a social institution in contrast to the other three kinds of relationships, and gender roles, are variables that interweave the discussion and evaluation of all relationships.

The next chapters describe and offer an analysis of major findings in the areas of money, work and sex. The conclusion analyzes the four kinds of relationships and points to the inherent strengths and vulnerabilities in all groupings. Finally, twenty relationships are described in a transcribed, personal accounting of intimate relationships, offering the reader a glimpse into five lives of each of the four kinds of couples.

The decision to include gay, lesbian and cohabitating couples in the study was valuable, since these groups have not been adequately studied. Including them shed light on imperatives created by both gender roles and marriage as an institutionally sanctioned form of relationship. Some of the findings, which are obvious, still warrant noting. The couples who are happiest share power, decision making, and the freedom to initiate sex. However, many marital relationships are threatened by shifts in the balance of power when women are career-oriented and vocationally successful. Although lasting relationships take place more in marriage than any other kind of relationship, the institution of marriage is shaken by impermanence. Relationships least likely to be sustained are those in which commitment to one another is undermined by fears of interdependence and mutual responsibility. Lasting and satisfying relationships reflect a wide range of lifestyle and personal choices.

Some further findings are: The institution of marriage is based on an unequal distribution of power between men and women. Although men may be giving up the sole provider role, they do not want to give up the privileges associated with the male role. Other forms of relationships have more equality, but have few prescribed roles, are not sanctioned by society, and offer less permanence. As women press for equality and seek changes in the balance of power, relationships are at greater risk.

Some of the findings lose their impact as the reader becomes flooded with seemingly endless data that overshadows the more meaningful conclusions. The book is long, and many sections are burdened with too many equally weighted findings. Reading the historical perspective, the conclusions, and skimming through the findings and some case examples is recommended.

Since the study is descriptive, it did not express any views on how to make things better. Yet some of its findings may help couples to benefit from working on areas of conflict and improving the quality of their relationship. Most significant are the changing roles of men and women in this society, which create a need for new accommodations, and ground rules that distribute power and control more equitably. The major universal finding remains constant: Caring, sharing, supporting, interdependence and commitment are basic foundations for permanent relationships among all groups.

While this work provides data on the diversity of couple relationships today, there are other knowledge bases such as those being developed in various family treatment models. These models need to be more widely described.

ZELDA FOSTER, MSW
Brooklyn Veterans Administration
Medical Center
New York, NY 11209

BOOKS RECEIVED

ANATOMY

Atlas of Human Cross-Sectional Anatomy. By Donald R. Cahill, PhD, Matthew J. Orlando, MD. 139 pp., illustrated. Philadelphia, PA, Lea & Febiger, 1984. $29.50 (hardcover).

CARDIOLOGY

Cardiovascular Rehabilitation: A Comprehensive Approach. Edited by Lysle H. Peterson, MD. 363 pp., illustrated. New York, NY, Macmillan Publishing Company, 1983. $42.00 (hardcover).

Drug Treatment of Heart Failure. Edited by Jay N. Cohn, MD. 210 pp., New York, NY, Yorke Medical Books, 1983. $35.00 (hardcover).

GASTROENTEROLOGY

The Crohn's Disease and Ulcerative Colitis Fact Book. National Foundation for Ileitis & Colitis. Edited by Peter A. Banks, MD, Daniel H. Present, MD, and Penny Steiner, MPH. 194 pp., New York, NY, Charles Scribner's Sons. 1983. $14.95 (hardcover).

GENETICS

The Gene Doctors: Medical Genetics at the Frontier. By Yvonne Baskin. 288 pp., New York, William Morrow and Company, 1984. $13.95 (hardcover).

HEALTH ADMINISTRATION

The Administration of a Public Health Agency: A case study of the New York City Department of Health. By Pascal James Imperato, MD. 226 pp., New York, NY, Human Sciences Press, Inc, 1983. $26.95 (hardcover).

Health and Health Care in New York City. By United Hospital Fund of New York. 105 pp., illustrated. New York, NY, United Hospital Fund of New York, 1984. $20 (softcover).

Patient-Centered Audit. By Christine G. Kruse, RN BSN, Silvia A. Maher, RN MN, Caroline Watson, ART. 70 pp., illustrated. St. Louis, MO, Warren H. Green, Inc, 1983. $14.50 (softcover).

Prospective Payment: What it is, How To Cope, Your Questions Answered. By The International Health Services, Ltd. 134 pp., Concord, MA, The International Health Services, Ltd., 1983. N/P (softcover).

HEMATOLOGY

Disseminated Intravascular Coagulation. Edited by T. Abe and M. Yamanaka, 352 pp., illustrated. Basel, Switzerland, Karger, 1983. $118.00 (hardcover).

HISTORY OF MEDICINE

Alexander Fleming: The Man and The Myth. By Gwen Macfarlane. 304 pp., Cambridge, MA, Harvard University Press, 1984. $20.00 (hardcover).

Evolution of the Department of Obstetrics And Gynecology at Downstate 1860–1980. By Leon C. Chesley, PhD. 96 pp., Brooklyn, NY, 1983.

Guinea Pig Doctors: The Drama of Medical Research Through Self-Experimentation. By Jon Franklin and John Sutherland, MD. 317 pp., New York, NY, William Morrow and Company, Inc, 1984. $15.95 (hardcover).

INFECTIOUS DISEASES

The Acquired Immune Deficiency Syndrome And Infections Of Homosexual Men. Edited by Pearl Ma, PhD, Donald Armstrong, MD. 442 pp., New York, NY, Yorke Medical Books, 1983. $39.95 (hardcover).

AIDS: The Medical Mystery. By Frederick P. Siegal, MD, Marta Siegal, MA. 269 pp., New York, NY, Grove Press, 1983. $19.50 (hardcover), $7.95 (softcover).

Fundamentals of Infection Control. Edited by Charles P. Craig, MD. 294 pp., Oradell, NJ, Medical Economics Books, 1983. $17.95 (softcover).

INTERNAL MEDICINE

Clinical Cardiovascular and Pulmonary Physiology. By Clive Rosendorff. 382 pp. New York, NY, Raven Press, 1983. $17.50 (softcover).

LABORATORY MEDICINE

Performance Standards for Laboratory Personnel. By William O. Umiker, MD and Susan M. Yohe. 160 pp., Oradell, NJ, Medical Economics Company. 1984. $13.95 (softcover).

LITERATURE AND MEDICINE

The Horror Of Life. By Roger L. Williams. 381 pp., Chicago, IL, The University of Chicago Press, 1980. N/P (softcover).

MISCELLANEOUS

The Healing Family: The Simonton Approach for Families Facing Illness. By Stephanie Matthews Simonton with Robert L. Shook. 276 pp., New York, NY, Bantam Books, 1984. $14.94 (hardcover).

RN's Sex Q & A: Candid Advice for You and Your Patients. By Dorothy DeMoya, RN MSN, Armando DeMoya, MD, Howard R. Lewis. 204 pp., Oradell, NJ, Medical Economics Books, 1983. $12.95 (softcover).

NUTRITION

Body Type Diet: And Lifetime Nutrition Plan. By Elliot D. Abravanel, MD, Elizabeth King. 256 pp., New York, Bantam Books, 1984. $3.95 (softcover).

Controversial Nutrition Policy Issues. Edited by Giorgio R. Solimano, MD, Sally A. Lederman, PhD. 429 pp., Springfield, IL, Charles C Thomas, 1983. $34.75 (hardcover).

OCCUPATIONAL MEDICINE

Workers At Risk: Voices from the Workplace. By Dorothy Nelkin, Michael S. Brown. 220 pp., Chicago, IL, The University of Chicago Press, 1984. $20.00 (hardcover).

ONCOLOGY

Environmental Aspects Of Cancer. The Role of Macro and Micro Components Of Foods. Edited by Ernst L. Wynder, MD, Gilbert A. Leveille, PhD, John H. Weisburger, PhD, MD, and G. E. Livingston, PhD. 294 pp., Westport, CT, Food & Nutrition Press, Inc, 1983. $65.00 (hardcover).

PAIN

Listen To Your Pain. By Ben E. Benjamin, PhD with Gale Borden, MD. 340 pp., illustrated. Middlesex, England, Penguin Books Ltd, 1983. $7.95 (softcover).

PATHOLOGY

Tumors. An Atlas of Differential Diagnosis. By Cyril Toker, MD. 496 pp., illustrated. Baltimore, MD, University Park Press, 1983. $65.00 (hardcover).

PEDIATRICS

Ambulatory Pediatrics III. By Morris Green, MD and Robert J. Haggerty, MD. 576 pp. Philadelphia, PA, W. B. Saunders Company, 1983. $45.00 (hardcover).

PHARMACOLOGY

The Doctor's Guide To Medication During Pregnancy And Lactation. By Larry H. Goldberg, MD, and Joann Leahy, MD. 252 pp., New York, NY, William Morrow and Company, Inc, 1984. $6.96 (softcover).

Drugs Used With Neonates And During Pregnancy. Second Edition. By Ina Lee Stile, Pharm.D, Thomas Hegyi, MD, I. Mark Hiatt, MD. 154 pp., Oradell, NJ, Medical Economics Books, 1984. $10.95 (softcover).

PSYCHIATRY

DSM-III Training Guide for Diagnosis of Childhood Disorders. By Judith L. Rapoport, MD, Deborah R. Ismond, MA. 178 pp., New York, NY, Brunner/Mazel Publishers, 1984. $17.50 (hardcover).

RADIOLOGY

Technological Basis of Radiation Therapy: Practical Clinical Applications. Edited by Seymour H. Levitt, MD, Norah DuV. Tapley, MD. 336 pp., illustrated. Philadelphia, PA, Lea & Febiger 1984. $45.00 (hardcover).

RHEUMATOLOGY

A Practical Handbook of Joint Fluid Analysis. By Robert A. Gatter, MD. 105 pp., illustrated. Philadelphia, PA, Lea & Febiger, 1984. $22.50 (hardcover).

SEXUALLY TRANSMITTED DISEASES

A Book About Sexually Transmitted Diseases. By Donna Cherniak. 52 pp., illustrated. Montreal, Canada, Montreal Health Press, Inc, 1983. $2.00 (softcover).

SPORTS MEDICINE

The Athletic Eye: Improved Sports Performance Through Visual Training. By Dr. Arthur Seiderman and Steven Schneider. 207 pp., illustrated. New York, William Morrow and Company, Inc, 1983. $14.95 (softcover).

SURGERY

A Short Textbook of Surgery. Fifth edition. By Selwyn Taylor, MCh, and Leonard Cotton, MCh. 631 pp., illustrated. New York, Arco Publishing, 1983. $16.50 (softcover).

Simple Surgical Emergencies. By Douglas Lindsey, MD. 262 pp., illustrated. New York, Arco Publishing, 1983. $12 (softcover).

In addition to these listings, the Journal will publish obituaries written by physician readers. Inquiries should first be made to the Editor.

Abraham Adnopoz, MD, Atlantic Beach. Died August 16, 1983; age 83. He graduated from the State University of New York Downstate Medical Center in 1924. Dr. Adnopoz was a Qualified Fellow of the International College of Surgeons, and his memberships included the Medical Society of the County of Kings and the Medical Society of the State of New York.

Albert Herman Aldridge, MD, Pinehurst, North Carolina. Died November 12, 1983; age 90. Dr. Aldridge graduated from the State University of New York Upstate Medical Center in 1918. He was a member of the New York County Medical Society and the Medical Society of the State of New York.

Minoru Araki, MD, East Meadow. Died November 3, 1983; age 63. He graduated from Boston University School of Medicine in 1953. Dr. Minoru was a Fellow of the American College of Pathologists and a Diplomate of the American Board of Pathology. His memberships included the New York State Society of Pathologists, the American Society of Clinical Pathologists, the American Public Health Association, the Nassau County Medical Society and the Medical Society of the State of New York.

Anthony Avata, MD, Manhasset. Died September 21, 1983; age 90. Dr. Avata graduated from the State University of New York Downstate Medical Center in 1916. He was a member of the New York County Medical Society and the Medical Society of the State of New York.

Horace Strow Baldwin, MD, Sarasota, Florida. Died October 27, 1983; age 88. Dr. Baldwin graduated from Cornell University Medical College in 1921 and was a member of the New York Medical Society and the Medical Society of the State of New York.

James Edward Baxter, MD, New York City. Died September 18, 1983; age 58. He was a 1951 graduate of Georgetown University School of Medicine. He was a Diplomate of the American Board of Psychiatry and Neurology. His memberships included the American Psychiatric Association, New York County Medical Society, and the Medical Society of the State of New York.

John Anthony Billows, MD, Hempstead. Died November 16, 1983; age 66. Dr. Billows graduated from New York Medical College, Flower and Fifth Avenue Hospitals in 1944. He was a Diplomate of the American Board of Radiology and a member of the Radiological Society of North America, Inc., the Nassau County Medical Society, and the Medical Society of the State of New York.

Joseph Thomas Birardi, MD, Auburn. Died October 17, 1983; age 55. Dr. Birardi attended Georgetown University School of Medicine and graduated in 1956. He was a Fellow of the American Academy of Family Practice and a Diplomate of the American Board of Family Practice. He was a member of the Medical Society of the County of Cayuga and the Medical Society of the State of New York.

Arthur I. Blieden, MD, New York City. Died November 5, 1983; age 72. Dr. Blieden graduated from the University of Cincinnati College of Medicine in 1936. He was a Fellow of the American College of Surgeons and a Diplomate of the American Board of Orthopedic Surgery. His memberships included the American Academy of Orthopaedic Surgeons, the American Academy of Compensation Medicine Inc., the New York County Medical Society, and the Medical Society of the State of New York.

Clarence Floyd Bratt, MD, Rochester. Died November 16, 1983; age 80. Dr. Bratt graduated from the University of Buffalo School of Medicine in 1928. His memberships included the Academy of Medicine, the American Academy of Family Practice, the American Geriatrics Society, the Medical Society of the County of Monroe, and the Medical Society of the State of New York.

Pyoung Ryoul Chang, MD, Cortland. Died October 4, 1983; age 47. Dr. Pyoung was a Fellow of the American College of Surgeons, a Fellow of the American College of Angiology, a Qualified Fellow of the International College of Surgeons, and a Diplomate of the American Board of Surgery. He was a member of the Cortland County Medical Society and the Medical Society of the State of New York.

Barnet Cooper, MD, New York City. Died September 29, 1983; age 74. Dr. Cooper attended the Middlesex University School of Medicine and graduated in 1943. He was a member of the American Academy of Family Practice, the New York County Medical Society and the Medical Society of the State of New York.

Michael William Damato, MD, Malverne. Died October 9, 1983; age 78. Dr. Damato graduated from the Universita Degli Studi di Roma, Facolta de Medicina e Chirurgia in 1934. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Stephanie Dessauer, MD, Woodstock. Died August 12, 1982; age 83. She graduated from Julius-Maximilian University Medical Fakultat, Wurzburg, Bavaria in 1925. Dr. Dessauer was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

William Thomas Ellis, MD, Jamestown. Died October 18, 1983; age 58. He was a graduate of the Albany Medical College of Union University in 1948. Dr. Ellis was a Fellow of the American College of Obstetricians and Gynecologists and a Diplomate of the American Board of Obstetrics and Gynecology. His memberships included the Academy of Medicine, the Medical Society of the County of Chautauqua and the Medical Society of the State of New York.

Edmund Deshields Evans, MD, Brooklyn. Died November 6, 1983; age 50. Dr. Evans graduated from Howard University College of Medicine in 1966. He was a Fellow of the American College of Obstetricians and Gynecologists and a Diplomate of the American Board of Obstetrics and Gynecology. His memberships included the Medical Society of the County of Kings and the Medical Society of the State of New York.

Robert B. Fath, MD, Scarsdale. Died October 9, 1983; age 60. He graduated from Cornell University Medical College in 1947. Dr. Fath was a Fellow of the American College of Physicians, a Diplomate of the American Board of Internal Medicine, and a Diplomate of the American Board of Nuclear Medicine. His memberships included the Academy of Medicine, the Society of Nuclear Medicine, the Medical Society of the County of Westchester, and the Medical Society of the State of New York.

Milton S. Fisher, MD, Brooklyn. Died November 26, 1983; age 71. He graduated from Howard University College of Medicine in 1938 and was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Frank Ward Goeller, MD, Coconut Creek, Florida. Died October 12, 1983; age 84. Dr. Goeller was a graduate of New York University College of Medicine in 1925. His memberships included the Suffolk County Medical Society and the Medical Society of the State of New York.

Raymond E. Goodrich, MD, Sun City West, Arizona. Died October 20, 1983; age 60. He graduated from McGill University Faculty of Medicine, Montreal, in 1945. Dr. Goodrich was a Fellow of the American College of Surgeons and a Diplomate of the American Board of Orthopedic Surgery. His memberships included the Academy of Medicine, the Suffolk County Medical Society, and the Medical Society of the State of New York.

Julius Caulkins Gray, MD, Chathamport, Maine. Died October 21, 1983; age 84. Dr. Gray graduated from the Columbia University College of Physicians and Surgeons. His memberships included the Medical Society of the County of Westchester, and the Medical Society of the State of New York.

Harry Gross, MD, New York City. Died August 26, 1983; age 82. Dr. Gross graduated from the Jefferson Medical College of Philadelphia in 1926. He was a Fellow of the American College of Cardiology, a Fellow of the American College of Physicians, and a Diplomate of the American Board of Internal Medicine. His memberships included the Academy of Medicine, the New York County Medical Society, and the Medical Society of the State of New York.

George W. Irmisch, MD, Johnstown. Died September 27, 1983; age 70. He graduated from Temple University School of Medicine, Philadelphia, in 1940. Dr. Irmisch was a Fellow of the American College of Surgeons, a Qualified Fellow of the International College of Surgeons, and a Diplomate of the American Board of Urology. His memberships included the American Urological Association, the American Geriatrics Society, the Pan American Medical Association, the Medical Society of the County of Fulton, and the Medical Society of the State of New York.

Nicholas Thomas Leone, MD, Brooklyn. Died November 3, 1983; age 60. He was a 1956 graduate of the Universita Degli Studi di Bologna, Facolta di Medicina e Chirurgia. Dr. Leone was a Fellow of the American College of Angiology. His memberships included the American Geriatrics Society, the International Society of Hematology, the Medical Society of the County of Kings, and the Medical Society of the State of New York.

Andrew B. LiMauro, MD, Staten Island. Died November 26, 1983; age 70. Dr. LiMauro was a graduate of the St. Louis University School of Medicine in 1939. He was a Diplomate of the American Board of Pediatrics, and his memberships included the American Academy of Pediatrics, the Richmond County Medical Society, and the Medical Society of the State of New York.

Gunther Lomnitz, MD, New York City. Died October 14, 1983; age 82. He graduated from Johann-Wolfgang-Goethe University Medical Fakultat, Frankfurt-Am-Main, Prussia in 1925. Dr. Lomnitz was a member of the New York Gastroenterological Society, New York County Medical Society, and the Medical Society of the State of New York.

James C. McGarvey, MD, Clearwater, Florida. Died November 5, 1983; age 79. He graduated from the University of Buffalo School of Medicine in 1931, and his memberships included the Medical Society of the County of Erie and the Medical Society of the State of New York.

Virginio Minervini, MD, New Fairfield, Connecticut. Died October 4, 1983; age 94. He was a graduate of Columbia University College of Physicians and Surgeons in 1913. Dr. Minervini was a Fellow of the American College of Surgeons, a Qualified Fellow of the International College of Surgeons, and was a member of the Academy of Medicine, the Medical Society of the County of Westchester, and the Medical Society of the State of New York.

Louis Nody, MD, Peekskill. Died October 26, 1983; age 72. Dr. Nody was a graduate of Kossuth Lajos Tudomanyegyetem Orvostudomanyi Fakultas, Debrecen in 1938. He was a member of the Academy of Medicine, the Medical Society of the County of Westchester, and the Medical Society of the State of New York.

John Edward O'Connor, MD, New York City. Died February 22, 1983; age 84. He graduated from the State University of New York Downstate Medical Center in 1934. Dr. O'Connor's memberships included the New York County Medical Society and the Medical Society of the State of New York.

John Mario Patrissi, MD, Bronx. Died November 13, 1983; age 72. He graduated from the Universita Degli Studi di Roma, Facolta di Medicina e Chirurgia in 1936. Dr. Patrissi was a member of the American Academy of Family Practice, the Bronx County Medical Society and the Medical Society of the State of New York.

Louis Perlman, MD, Brooklyn. Died August 26, 1983; age 83. Dr. Perlman graduated from the State University of

New York Downstate Medical Center in 1925. His memberships included the American Geriatrics Society, the Medical Society of the County of Kings, and the Medical Society of the State of New York.

Alexander S. Perry, MD, Woodside. Died November 2, 1983; age 69. Dr. Perry graduated from the Vytauto Didziojo Universiteto Medicinos Fakulteto, Kaunas in 1940. He was a member of the American Academy of Family Practice, the Medical Society of the County of Queens, and the Medical Society of the State of New York.

George Porter Robb, MD, Englewood, Florida. Died November 6, 1983; age 85. He graduated from Indiana University of Medicine in 1926 and was a member of the New York County Medical Society and the Medical Society of the State of New York.

Quintin Rosenthal, MD, New York City. Died August 8, 1983; age 74. Dr. Rosenthal graduated from the State University of New York Downstate Medical Center in 1935 and was a member of the New York County Medical Society and the Medical Society of the State of New York.

Rosario Rotolo, MD, Brooklyn. Died September 16, 1983; age 64. He graduated from Middlesex University School of Medicine in 1943 and was a Fellow of the American Academy of Family Practice. His memberships included the American Geriatrics Society, the Medical Society of the County of Kings, and the Medical Society of the State of New York.

Edwin I. Shack, MD, West Babylon. Died September 25, 1983; age 89. Dr. Shack graduated from the State University of New York Downstate Medical Center in 1916. His memberships included the Academy of Medicine, the Suffolk County Medical Society and the Medical Society of the State of New York.

Samuel Sheinkman, MD, New York City. Died October 24, 1983; age 64. He graduated from the Université de Lausanne Faculté de Medecine in 1955. Dr. Sheinkman was a member of the American Psychiatric Association, the American Society of Adolescent Psychiatry, the New York County Medical Society, and the Medical Society of the State of New York.

Mary H. Spalding, MD, Freeport. Died August 10, 1983; age 67. She was a graduate of the New York University College of Medicine in 1942. Dr. Spalding was a Fellow of the American College of Obstetricians and Gynecologists and a member of the New York County Medical Society and the Medical Society of the State of New York.

Edward F. Tartaglione, MD, Long Island City. Died October 23, 1983; age 77. Dr. Tartaglione attended Georgetown University School of Medicine and graduated in 1931. He was a Fellow of the American College of Obstetricians and Gynecologists, a Qualified Fellow of the International College of Surgeons, and a Diplomate of the American Board of Obstetrics and Gynecology. His memberships included the Medical Society of the County of Queens and the Medical Society of the State of New York.

Harvey J. Tompkins, MD, New York City. Died October 26, 1983; age 77. He graduated from the Stritch School of Medicine of Loyola University, Chicago in 1932. Dr. Tompkins was a Fellow of the American College of Physicians, a Fellow of the American Psychiatric Association, and a Diplomate of the American Board of Psychiatry and Neurology. His memberships included the Academy of Medicine, the American Academy of Neurology, New York County Medical Society, and the Medical Society of the State of New York.

Roswald G. Turner, MD, Reading, Pennsylvania. Died November 21, 1982; age 82. He graduated from the University of Arkansas School of Medicine in 1925 and was a member of the Medical Society of the County of Chemung and the Medical Society of the State of New York.

Arnulfo D. Villanueva, MD, New York City. Died December 30, 1982; age 53. He was a graduate of the Universidad de Santo Domingo Facultad de Medicina in 1956 and was a member of the New York County Medical Society and the Medical Society of the State of New York.

Alexander Zimany, MD, Monroe, Connecticut. Died October 28, 1983; age 79. Dr. Zimany attended the Columbia University College of Physicians and Surgeons and graduated in 1929. He was a Diplomate of the American Board of Plastic Surgery. His memberships included the American Society of Plastic and Reconstructive Surgery, the New York County Medical Society, and the Medical Society of the State of New York.

CORRECTION

In the Obituaries of the January issue of the *Journal*, the correct date of death of William Dailey Dunaway, MD is December 26, 1982.

Guidelines for authors

ORIGINALITY

The *New York State Journal of Medicine* welcomes research papers and original essays on the practice of medicine, medical education, public health, the history of medicine, medicolegal matters, legislation, ethics, the mass media and socioeconomic issues in health care.

Manuscripts should be prepared according to the "Uniform requirements for manuscripts submitted to biomedical journals" (*NY State J Med* 1983; 83:1089–1094). The requirements were established by the International Committee of Medical Journal Editors, of which the *Journal* is a participating member. These Guidelines are intended to highlight aspects of the *Journal*'s particular style of publication.

A manuscript will be considered for publication if it is original, has not been published previously in whole or in part in either a medical journal or a lay publication, and is not simultaneously under consideration elsewhere. A copy of any possibly duplicative material, such as a reference "in press," should be submitted along with the manuscript.

PREPARATION

An original typewritten or "word-processed" manuscript and two photocopies (to facilitate outside review) are required. If the manuscript is not accepted for publication, the original and one copy will be returned. All figures must be submitted in triplicate. The manuscript should be double-spaced throughout, including references, tables, legends, quotations, and acknowledgments. A separate title page should include the full title of the paper in upper and lower case type, the names of the authors exactly as they should appear in print (including their highest academic degree), an abbreviated title of no greater than 40 spaces for use as a running foot, and the names of all providers of funding for research on which the paper is based. Information on the amount and allocation of funding is optional.

A corresponding author should be designated in the covering letter. Authors should list their title and affiliation at the time they did the work, and, if different, their present affiliation. The addresses and telephone numbers of all authors should be supplied for editorial purposes. All authors of a manuscript are responsible for having read and approved it for submission.

CATEGORIES

Research Papers should be limited to 2,500 words and should include the following sections: Introduction, Methods, Results, Discussion, and References. Multiple subheadings and numbered lists are discouraged. An abstract limited to 150 words should state the reasons for the study, the main findings, and their implications. Statistical evaluations should be described in the Methods section, and the name and affiliation of the statistician should be included in the acknowledgments if this individual is not listed as a coauthor. Reports of experiments involving human subjects must include a description in the Methods section of the informed consent obtained and a statement that the procedures followed were approved by an institutional research review committee. Anonymity of patients must be preserved. Reports of experiments on animals must note which guidelines were followed for the care and use of laboratory animals.

Case Reports should be limited to 1,250 words. Review Articles should not exceed 3,000 words. Commentaries should be between 750 and 1,000 words. Other kinds of original essays should not exceed 2,000 words. A letter of inquiry should be sent to the editor prior to submitting a Review Article or Commentary.

For Research Papers only, scientific measurements should be given in conventional units, with Système Internationale (SI) units in parentheses. Abbreviations and acronyms should be kept to a minimum, and jargon should be avoided. Generic names of drugs should be used instead of brand names.

FIGURES

The submission of color illustrations or slides is discouraged. Only black and white glossy photographic prints or "camera-ready" artwork will be accepted. The *Journal* is unable to provide art services such as the addition of arrows to photographs. A signed consent for publication must accompany photographs in which the patient is identifiable. Illustrations from other publications generally will not be considered. Legends for illustrations should be typed on a separate sheet, and for photomicrographs should include magnification and stain. Each illustration should be lightly marked on the back in pencil with the name of the first author, the number as cited in the text, and an arrow indicating the top. Each set of illustrations should be submitted unmounted in a separate envelope.

Tables should be simple, self-explanatory, and few in number. Each table should be typed double-spaced on a separate sheet.

REFERENCES

References should be limited to the most pertinent. The recommended maximum number of references is 25 for Research Papers and most other original contributions (except lengthier Review Articles), 12 for Commentaries and Case Reports, and six for letters to the editor.

Authors are responsible for the accurate citation of references. Citation of secondary sources is discouraged except where the original reference is unobtainable. Authors may not cite references they have not read, and the use of abstracts as references should be avoided.

References should be indicated in the text by superscript numbers following the name of the author (eg, Smith^2 reported two cases).

The list of references at the end of the article should be typed double-spaced and references should be numbered in the order in which they appear on the text. When there are six or fewer authors, all should be listed; where there are seven or more, the first three should be listed, followed by *et al.* Names of journals should be abbreviated according to *Index Medicus* and underlined.

Sample references:

1. Kepes ER, Thomas P, Vemulapalli K: Methadone and intravenous morphine requirements. *NY State J Med* 1983; 83:925–927.
2. McGuigan JE. Peptic ulcer. In: Petersdorf RG, Adams RD, Braunwald E, Isselbacher KJ, Martin JB, Wilson JD, eds. *Harrison's Principles of Internal Medicine*. New York, McGraw-Hill, 1983, pp 1697–1712.

REVIEW

All manuscripts are reviewed by the editors, and most manuscripts are sent to outside referees. Decisions concerning acceptance, revision, or rejection of a manuscript are usually made within three to six weeks. Every effort will be made to assure prompt publication of an accepted manuscript. A galley proof will be sent to the author for approval prior to publication.

Address correspondence to Alan Blum, MD, Editor, *New York State Journal of Medicine*, P.O. Box 5404, 420 Lakeville Road, Lake Success, NY 11042.

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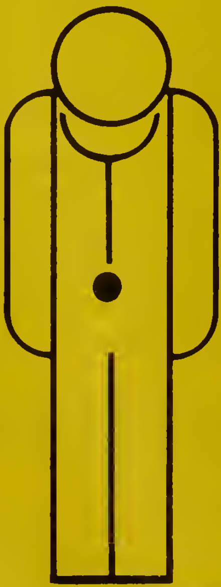

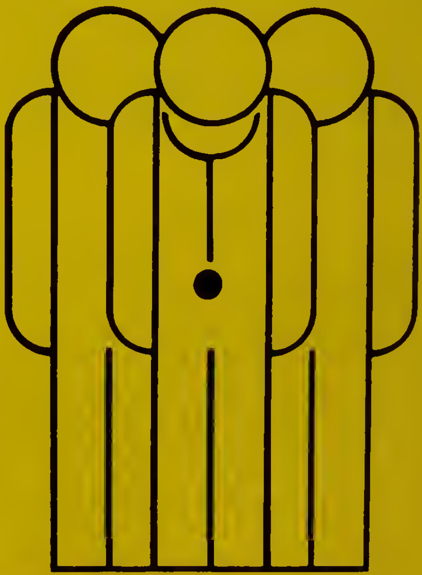

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1984 ANNUAL CME ASSEMBLY

Medicine in this Age of Violence

PRESENTED BY THE

Medical Society of the State of New York

JUNE 29 - JULY 1

Sheraton Centre
Seventh Ave. & 52nd St.
New York City

☐

HIGHLIGHTS . . .

General Session: Medicine in this Age of Violence • 26 Sessions • Panel Discussions • Meet the Professor • Scientific & Technical Exhibits • Medical Society Reception

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Medical Society
of the
State of New York
June 29–July 1, 1984

Reservations must be received by hotel no later than June 8.
IF RATE REQUESTED IS NOT AVAILABLE, NEXT AVAILABLE RATE WILL APPLY, RESERVATIONS RECEIVED AFTER SPECIFIED DATE WILL BE ACCOMMODATED ON A RATE AND SPACE AVAILABILITY BASIS ONLY.

Checkout time is 1:00 p.m. Normal Check in time is after 3:00 p.m.

Reservations are held until 6:00 p.m. unless guaranteed by a one nights deposit or guaranteed with one of the following credit cards: Diners Club, Carte Blanche, American Express.

Credit Card # ________________ Exp. date ________ Type ________

General Information

Our CME Sessions are open to all physicians and the allied professions. The three full days of meetings will provide the individual physician with a possible 25 credits out of a total of 100, Category 1, CME credit hours being offered. Over 120 outstanding speakers, including a number from out-of-state, will present papers at 26 sessions. A highlight of the Assembly will be a general session on "Medicine in this Age of Violence," to be presented on Saturday, June 30th. Some areas to be discussed will be violence on the highway, in sports, in institutions, in war, sexual abuse of children, and drug abuse in adolescents.

Returning by popular request, "Meet the Professor" sessions will take place on Friday, June 29th. There will be six, 1½ hour sessions scheduled throughout the day.

Our program covers a wide range of medical specialties and focuses on helping the practicing physician meet the daily needs of patient care. You can be assured of an interesting program.

In addition, there will be Scientific and Technical Exhibits on display to update the physician on developments in both areas. Complimentary coffee breaks will be scheduled in the mornings and afternoons to allow time for physicians to visit the exhibits.

A reception for physicians and exhibitors, compliments of the Medical Society of the State of New York, will be held on Friday, June 29, from 6-7 pm. As the Assembly date closely precedes the 4th of July, we suggest that you bring your family to enjoy a pre-holiday weekend in New York City before continuing to your destination. The Sheraton Centre provides valet parking for your convenience.

Among the many new attractions in New York City are the downtown *South Street Seaport Museum,* a restoration of the early 19th century seaport that was engaged in trade and commerce. Here we find historic sailing ships at Pier 16, a multi-screen movie presentation of the early trading days, the Fulton Market with its restaurants, cafes, food shops, plus many specialty shops in the area. Uptown on Fifth Ave., the new *Trump Tower* presents a breathtaking, multilevel atrium lobby lined in pink marble, waterfalls and tropical plants. Escalators take you to international shops on each level. Visit the legendary WWII Aircraft Carrier *Intrepid, Sea-Air Space Museum* at Pier 86, a must experience for the entire family. Bring your family and join your colleagues for a weekend of stimulating CME sessions.

HOTEL RESERVATIONS

Physicians must make their own hotel reservation no later than June 8, 1984. If making reservations by telephone, please identify the Medical Society meeting for the special rate to apply.

REGISTRATION

Registration will take place in the Exhibition Centre, located on the lower level of the hotel. For those who registered in advance, your ID Badge will be held at the Medical Society Registration Desk. All new registrants must present identification at the registration desk.

REGISTRATION HOURS

Friday & Saturday —
8:30 a.m.-5:00 p.m.
Sunday — 8:30 a.m.-4:30 p.m.

MEETING HOURS

Friday — Meet the Professor,
8:30 a.m.-5:30 p.m.
All other meetings,
9:00 a.m.-5:00 p.m.
Saturday & Sunday —
9:00 a.m.-5:00 p.m.

PRELIMINARY PROGRAM
1984 ANNUAL CME ASSEMBLY

Medical Society of the State of New York

The Sheraton Centre
New York City

June 29–July 1, 1984

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REGISTRATION

Registration is open to MSSNY members and their guests, nonmember physicians, and members of the allied professions. There is a registration fee.

An advance registration form will be found in this issue. For those who register in advance, your identification badge will be held at the MSSNY Registration Desk located in the Exhibition Centre, lower lobby of the Sheraton Centre. For those who have not registered in advance, registration will take place Friday and Saturday, June 29 and 30th from 8:30 a.m. to 5:00 p.m., and Sunday, from 8:30 a.m. to 4:30 p.m. All meetings and exhibits will close at 5:00 p.m. on Sunday.

Identification badges or buttons are required for admittance to all CME meetings and exhibits. It is imperative that each registrant show identification at the registration desk before a badge or button is issued. We ask that you wear your identification at all times while in the meeting and exhibit areas. These measures are taken to ensure that your meeting will be a professional one and not available to anyone who may walk in from the street.

CME SESSIONS

General Sessions will be held on Friday, June 29, from 9:00 a.m. to 1:00 p.m.; on Saturday, June 30, from 9:00 a.m. to 12:00 Noon and from 2:00 p.m. to 5:00 p.m.; and on Sunday, July 1, from 9:00 a.m. to 1:00 p.m. and from 2:00 p.m. to 5:00 p.m.

Section meetings will be held on Friday, June 29, from 9:00 a.m. to 12:00 Noon and from 2:00 p.m. to 5:00 p.m.; on Saturday, June 30, from 9:00 a.m. to 12:00 Noon and from 2:00 p.m. to 5:00 p.m.; and Sunday, July 1, from 9:00 a.m. to 1:00 p.m. and 2:00 p.m. to 5:00 p.m.

"Meet the Professor" sessions will take place on Friday, June 29th, from 8:30 a.m. to 5:30 p.m. There will be six, 1½ hour sessions scheduled throughout the day.

CME CREDITS

The Medical Society of the State of New York, as an organization accredited for CME, designates this continuing medical education activity as meeting the criteria for the designated number of credit hours in Category 1 of the Physician Recognition Award of the AMA, and/or MSSNY's Method 6.

Each program is acceptable for prescribed or personal interest credits by the American Academy of Family Physicians (AAFP) as designated.

The Medical Society of the State of New York CME credit forms will be issued at the entrance to each meeting room at the opening of each program.

EXHIBITS

Scientific and Technical Exhibits will be located in the Exhibition Centre, lower level of the Sheraton Centre. Exhibits will be on view Friday, Saturday and Sunday, June 29–July 1, from 8:30 a.m. to 5:00 p.m.

PHYSICIAN MESSAGE CENTER

Messages for physicians may be left at the Information Desk at the Medical Society registration area. The names of those for whom messages have been received will be posted on a board at the MSSNY registration area in the Sheraton Exhibition Centre.

COFFEE BREAKS

Coffee breaks, compliments of the Medical Society of the State of New York, will be held on Friday, Saturday and Sunday from 10:30 a.m.-11:30 a.m. and from 3:00 p.m.-4:00 p.m. in the Exhibition Centre located on the lower level of the hotel.

RECEPTION

A reception, sponsored by the MSSNY, will be held in the Princess Ballroom at the Sheraton Centre on Friday, June 29th from 6:00 p.m.-7:00 p.m. Members, spouses and exhibitors are cordially invited. Your identification badge must be presented at the door.

1984 ANNUAL CME ASSEMBLY

Medical Society of the State of New York
Sheraton Centre, New York City

FRIDAY, JUNE 29

Morning
Cardiovascular Diseases, Royal Ballroom A
Cancer Update, Versailles Terrace
Pediatrics/School Health, Royal Ballroom B (all day)
Meet the Professor, Consulate Suite
Regency Foyer

Afternoon
Pediatrics/School Health, Royal Ballroom B
Neurosurgery, Versailles Terrace
Medical Legal & Workers' Compensation/Occupational Medicine, Royal Ballroom A
Neurology, Regency Ballroom
Meet the Professor, Consulate Suite
Regency Foyer

SATURDAY, JUNE 30

Morning
Chest Diseases, Regency Ballroom
Internal Medicine, Georgian Ballroom A (all day)
Ophthalmology, Royal Ballroom A (all day)
General Session "Violence", Georgian Ballroom B (all day)
Obstetrics/Gynecology, Versailles Terrace
Hand Surgery, Royal Ballroom B (all day)

Afternoon
Internal Medicine, Georgian Ballroom A
Ophthalmology, Royal Ballroom A
General Session "Violence", Georgian Ballroom B
Dermatology/Otolaryngology, Versailles Terrace
Pathology/Gastroenterology, Regency Ballroom
Hand Surgery, Royal Ballroom B

SUNDAY, JULY 1

Morning
Allergy & Immunology, Georgian Ballroom A
Family Practice/Preventive Medicine/Psychiatry, Royal Ballroom B (all day)
Orthopedic Surgery/General Surgery/Plastic Surgery/Physical Medicine & Rehabilitation/Radiology/Anesthesiology, Georgian Ballroom B (all day)
Urology/Emergency Medicine, Royal Ballroom A
Women's Medical Society of New York State, Versailles Terrace

Afternoon
Family Practice/Preventive Medicine/Psychiatry, Royal Ballroom B
Orthopedic Surgery/General Surgery/Plastic Surgery/Physical Medicine & Rehabilitation/Radiology/Anesthesiology, Georgian Ballroom B
Alcoholism, Royal Ballroom A

◆

CME CREDITS: Each program will be eligible for CME Category 1 credits on an hour-for-hour basis.

◆

Technical & Scientific Exhibits

1984 ANNUAL CME ASSEMBLY

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Otolaryngology—Head & Neck Surgery

STEVEN PARNES, M.D., Albany, Chairman
PAUL HARRINGTON, M.D., Rochester, Program President
STEVEN PARNES, M.D., Albany, Secretary
FOUAD MICHAEL, M.D., Garden City, Delegate

Pathology, Clinical Pathology & Blood Banking

PRIMITIVO CRUZ, M.D., Norwich, Chairman
MARIO B. ROSSI, M.D., Oyster Bay, Vice-Chairman
LOUIS G. JAKOVIC, M.D., Albany, Secretary
HERBERT LANSKY, M.D., Eggertsville, Delegate

Pediatrics

MARTIN C. USHKOW, M.D., Syracuse, Chairman
PHILIP W. H. ESKES, M.D., Huntington, Vice-Chairman
LOUIS COOPER, M.D., New York City, Secretary
DAVID ANNUNZIATO, M.D., East Meadow, Delegate

Physical Medicine & Rehabilitation

CATALINO C. DAROY, M.D., Schenectady, Chairman
DAVID H. BROOKS, M.D., New York City, Vice-Chairman
MIRIAM LANE, M.D., Scarsdale, Secretary
DAVID ERNSTOFF, M.D., Great Neck, Delegate

Plastic, Reconstructive & Maxillofacial Surgery

ROBERT W. BERNARD, M.D., White Plains, Chairman
CLOYD KERCHNER, M.D., Glenn Falls, Vice-Chairman
DONALD WOOD SMITH, M.D. New York City, Secretary
PHILIP C. BONANNO, M.D., White Plains, Delegate

Preventive Medicine & Public Health

WILLARD C. SCHMIDT, M.D., Ithaca, Chairman
DONALD B. THOMAS, M.D., Tonawanda, Vice-Chairman
RUSSELL C. JOHNSON, M.D., Goshen, Delegate

Psychiatry

LEONARD KANE, M.D., Brooklyn, Chairman
RICHARD DROOZ, M.D., New York City, Vice-Chairman
JOHN CASARINO, M.D., New York City, Secretary
JEROME SILVERMAN, M.D., New York City, Delegate

Radiology

RITA F. GIROLAMO, M.D., Valhalla, Chairman
VICTOR PANARO, M.D., Amherst, Delegate

School Health

MARTIN C. USHKOW, M.D., Syracuse, Chairman
RAYMOND J. CASSADY, M.D., Syracuse, Vice-Chairman
STEPHEN H. MINTZ, M.D., Syracuse, Secretary
MARTIN C. USHKOW, M.D., Syracuse, Delegate

Surgery

J. RAYMOND HINSHAW, M.D., Rochester, Chairman

Urology

IRWIN FRANK, M.D., Rochester, Chairman
PELLIGRINO TOZZO, M.D., New Rochelle, Vice-Chairman
ANDREW McGOWAN, Jr., M.D., Rockville Centre, Secretary
LAWRENCE RAVICH, M.D., Bethpage, Delegate

■ All papers read before the Society become the property of the Society. The original copy of each paper shall be left with the Secretary of the Section.

The American Association of Medical Assistants, New York State Society, Inc., will be on hand to answer questions concerning certified medical assistants for the doctor's office. Their table will be located just inside the entrance to the exhibit hall.

FRIDAY, JUNE 29, 1984

MEET THE PROFESSOR

Planned and Organized by Maxwell Spring, M.D., Associate Chairman, Scientific Program Committee
Clinical Associate Professor of Medicine, New Jersey Medical School

8:30 A.M.-5:30 P.M.
CONSULATE SUITE
REGENCY FOYER

CONTINUING MEDICAL EDUCATION CREDIT:
AMA, PRA, 1½ Hours, Category 1; Per Session
AAFP, 1½ Hours, Prescribed

An opportunity to meet informally and discuss clinical problems on a one-to-one basis with experts in your field.

8:30 A.M. **Calcium Blockers**

STEPHEN SCHEIDT, M.D., New York City

Professor of Clinical Medicine,
New York Hospital-Cornell Medical Center

Objective: To update the practicing physician on current knowledge concerning calcium blockers, including new data on arrhythmias, vasospastic angina, chronic stable angina, IHSS, hypertension, and other current or potential indications for their use.

10:00 A.M. **Management of Chronic Cardiac Failure**

RICHARD GORLIN, M.D., New York City

Professor and Chairman of Medicine,
Mount Sinai Hospital

Objective: The causes of heart failure and certain compensatory mechanisms which are called into play to alleviate it will be discussed, particularly as they relate to chronic heart failure.

11:30 A.M. **Update of Clinical Gastroenterology**

HOWARD M. SPIRO, M.D., New Haven, Connecticut

Professor of Medicine, Yale University School of Medicine

Objective: Update the practicing physician on clinical and technological advances in gastroenterology while keeping the patient's problem as a focus.

1:00 P.M. **Progress in the Management of Renal Insufficiency**

ELI A. FRIEDMAN, M.D., Brooklyn

Professor of Medicine, Chief, Division of Renal Disease,
State University of New York Downstate Medical Center

Objective: Uremia therapy is one of the great successes of this century. There are currently more than 250,000 patients sustained by maintenance hemodialysis, peritoneal dialysis, and renal transplantation. The importance of identification and appropriate preparation of candidates for these therapies is self evident. The major causes of renal failure, its conservative management, and the advantages and problems of each therapeutic option will be considered.

2:30 P.M. **Management of Diabetes**

PHILIP FELIG, M.D., New Haven, Connecticut

Professor of Medicine and Chief of Endocrinology,
Yale University School of Medicine

Objective: This session will deal with newer intensive approaches to the management of diabetes, including self-monitoring of blood glucose, multiple insulin injections and insulin pump therapy.

4:00 P.M. **Update on Cephalosporins**

HAROLD NEU, M.D., New York City

Professor of Medicine and Pharmacology;
Chief, Division of Infectious Diseases,
Columbia University College of Physicians and Surgeons

Objective: This lecture will attempt to place all of the cephalosporin antibiotics in perspective so that the practicing physician will know when to use these drugs.

(continued)

Cardiovascular Diseases
Jointly Sponsored by the New York Cardiological Society

9:00 A.M.–1:00 P.M.
ROYAL BALLROOM A

CONTINUING MEDICAL EDUCATION CREDIT:
AMA, PRA, 4 Hours, Category 1; AAFP, 3½ Hours, Prescribed

AN UPDATE ON THE NON-SURGICAL TREATMENT MODALITIES IN CARDIOVASCULAR DISEASES

MOHAMMED ZAHIR, M.D., Brooklyn, *Moderator*

Director of Medicine, and Chief of Cardiology, Kingsbrook Jewish Medical Center; Clinical Associate Professor of Medicine, State University of New York, Downstate Medical Center

Objective: The participants will be informed of recent developments in major non-surgical treatment modalities in cardiovascular diseases. They will learn about the use of angioplasty, vasodilators, thrombolytic therapy, calcium channel blockers, beta blockers and exercise training in the management of cardiovascular diseases.

9:00 A.M. **Use of Beta Blockers, Calcium Channel Blockers, and Thrombolytic Agents in the Management of Acute Myocardial Infarction**

HILTRUD S. MUELLER, M.D., Bronx

Associate Chief of Cardiology, Montefiore Hospital; Professor of Medicine, Albert Einstein College of Medicine of Yeshiva University

9:45 A.M. **Use of Vasodilators in the Management of Congestive Heart Failure**

LAWRENCE A. GOULD, M.D., Brooklyn

Chief, Division of Cardiology, The Methodist Hospital; Clinical Professor of Medicine, State University of New York Downstate Medical Center

10:30 A.M. **Coffee Break to View Exhibits**

10:50 A.M. **Current Status of Coronary Angioplasty in the Management of Coronary Artery Disease**

KENNETH MITCHELL KENT, M.D., Washington, DC

Director, Cardiac Catheterization Laboratories; Associate Clinical Professor of Medicine, Georgetown University Medical Center

11:30 A.M. **Role of Exercise in the Treatment Program of Patients with Coronary Heart Disease**

RICHARD A. STEIN, M.D., Brooklyn

Associate Professor of Medicine, State University of New York Downstate Medical Center

12:10 P.M. **Panel Discussion**

The Above Speakers

GENERAL SESSION
Cancer Update 1984
Radiology
Internal Medicine

9:00 A.M.–1:00 P.M.
VERSAILLES TERRACE

CONTINUING MEDICAL EDUCATION CREDIT:
AMA, PRA, 4 Hours, Category 1; AAFP, 3½ Hours, Prescribed

CANCER UPDATE—1984

MARTIN LIPKIN, M.D., New York City, *Moderator*

Associate Chairman, Scientific Program Committee, Medical Society of the State of New York; Professor of Medicine, Cornell University Medical College; Attending Physician, Department of Medicine, Memorial Sloan-Kettering Cancer Center

Objective: This general session will cover the most recent advances in diagnosis and treatment of breast, pancreatic, colon and childhood cancers, including NMR (Nuclear Magnetic Resonance), and will discuss supportive cancer care facilities in the community.

9:00 A.M. **Breast Cancer: Diagnostic Modalities**

RITA F. GIROLAMO, M.D., Valhalla

Professor and Vice Chairman, Department of Radiology, New York Medical College

9:25 A.M. **Breast Cancer: Surgical Treatment**

DAVID KINNIE, M.D., New York City

Chief of Breast Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center

(continued)

9:50 A.M. **Breast Cancer: Chemotherapy**

Franco Muggia, M.D., New York City

Professor of Medicine and Clinical Director, Cancer Center, New York University Medical Center

10:15 A.M. **Pancreatic Cancer**

Emil Balthazar, M.D., New York City

Professor of Radiology, New York University Medical Center

10:40 A.M. **Coffee Break to View Exhibits**

11:00 A.M. **Nuclear Magnetic Resonance (NMR): Present and Future Applications**

Yahya Berkmen, M.D., New York City

Professor of Radiology, New York Hospital-Cornell Medical Center

11:30 A.M. **Treatment of Metastatic Colon Cancer**

Moshe Shike, M.D., New York City

Assistant Attending Physician, Memorial Sloan-Kettering Cancer Center

12:00 NOON **Malignancy in Children**

Lawrence Helson, M.D., New York City

Associate Professor; Attending Pediatrician; Memorial Sloan-Kettering Cancer Center

12:30 P.M. **Supportive Cancer Care**

Ms. Nessa Coyle, R.N., New York City

Director, Supportive Care Program, Department of Neurology, Memorial Sloan-Kettering Cancer Center

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Pediatrics/School Health
Joint Meeting With
American Academy of Pediatrics, District II

9:00 A.M.–5:00 P.M.
ROYAL BALLROOM B

CONTINUING MEDICAL EDUCATION CREDIT: AMA, PRA, 4 Hours, Category 1; AAFP, 4 Hours, Prescribed

VIOLENCE AND ABUSE

Martin C. Ushkow, M.D., Syracuse, *Moderator*

Clinical Assistant Professor of Pediatrics, State University of New York Upstate Medical Center; Medical Director, Syracuse City School District, Chairman, Sections on Pediatrics and School Health, Medical Society of the State of New York

Objective: To educate the physician about violence and abuse of children. Clinical applications and the role of the Health Department.

9:00 A.M. **Introduction and Welcome**

Martin C. Ushkow, M.D., Syracuse

9:05 A.M. **The Sexual Misuse of Children: A Spectrum of the Problem**

Margaret McHugh, M.D., New York City

Clinical Associate Professor, New York University School of Medicine; Director, Adolescent Ambulatory Services, Bellevue Hospital Center

9:40 A.M. **Clinical Implications of Depression in Abused and Neglected Children**

Marvin L. Blumberg, M.D., Jamaica

Chairman, Department of Pediatrics, The Jamaica Hospital; Clinical Associate Professor, State University of New York at Stony Brook

10:15 A.M. **The Role of the New York State Department of Social Services**

Ms. Diana Malkonian

Director, Child Abuse and Maltreatment State Central Register, New York State

10:45 A.M. **Coffee Break to View Exhibits**

11:15 A.M. **Child Abuse: Prevention, Hope, or Reality**

James S. Cameron, M.S.W.

Executive Director, New York State Federation on Child Abuse and Neglect

12:00 NOON **Lunch and Visit the Exhibits**

2:00 P.M.–5:00 P.M.

2:00 P.M. **Domestic Violence and Child Abuse Using a technique called role playing to portray mental health situations, the players present vignettes to cover the theme.**

Utica/Marcy Mental Health Players

3:15 P.M. **Coffee Break to View the Exhibits**

3:45 P.M. **American Academy of Pediatrics, District II Meeting All Academy of Pediatrics members are invited.**

James G. Lione, M.D., Flushing, *Chairman*

(*continued*)

Neurology

2:00 P.M.–5:00 P.M.
REAGENCY BALLROOM

CONTINUING MEDICAL EDUCATION CREDIT:
AMA: PRA, 3 Hours, Category 1; AAFP, 2½ Hours, Prescribed

A SYMPOSIUM ON DEMENTIAS

DAVID GREEN, M.D., Troy, *Moderator*
Clinical Professor of Neurology, Albany Medical College of Union University, Albany

Objective: The Symposium will deal with the clinical study and management of a demented patient. A practical clinical approach will be emphasized. The differential diagnosis and the remedial courses of dementia will be given first priority.

2:05 P.M. **Post-traumatic Dementia**
JERID FISHER, Ph.D., Troy
Program Director, Head Injury Center at Highgate Manor

2:35 P.M. **Question and Answer Period**

2:45 P.M. **Dementia Versus Depression**
JOHN A. O'SULLIVAN, M.D., Rochester
Clinical Assistant Professor of Neurology, University of Rochester School of Medicine and Dentistry

3:15 P.M. **Question and Answer Period**

3:25 P.M. **Coffee Break to View Exhibits**

3:40 P.M. **Normal Pressure Hydrocephalus: An Enigma**
RICHARD SATRAN, M.D., Rochester
Professor of Neurology, University of Rochester School of Medicine and Dentistry

4:10 P.M. **Question and Answer Period**

4:20 P.M. **Remedial Causes of Dementia**
DAVID O. MARSH, M.D., Rochester
Associate Professor of Neurology, University of Rochester School of Medicine and Dentistry

4:50 P.M. **Question and Answer Period**

Neurosurgery

2:00 P.M.–5:00 P.M.
VERSAILLES TERRACE

CONTINUING MEDICAL EDUCATION CREDIT:
AMA, PRA, 3 Hours, Category 1; AAFP, 2½ Hours, Prescribed

CENTRAL NERVOUS SYSTEM TRAUMA

A. JOHN POPP, M.D., Albany, *Moderator*
Associate Professor, Neurosurgery, Albany Medical College of Union University; Chief, Neurosurgical Section, Albany Veterans Administration Hospital

Objective: In the spectrum of organ systems injury, brain and spinal cord trauma is of primary importance because of its frequency and long-term consequences. This program reviews clinical and research topics dealing with central nervous system trauma to emphasize the current work being done in the field.

2:05 P.M. **Treatment of Head Injuries in the 16th and 17th Centuries**
LOUIS BAKAY, M.D., Buffalo
Professor and Chairman, Division of Neurosurgery, State University of New York at Buffalo

2:30 P.M. **The Clinical and Experimental Pathology of Brain Trauma**
KEVIN D. BARRON, M.D., Albany
Professor and Chairman, Department of Neurology; Professor, Pathology, Albany Medical College of Union University

3:00 P.M. **Coffee Break to View Exhibits**

3:20 P.M. **Violence Against Children**
DEREK A. BRUCE, M.D., Philadelphia, Pennsylvania
Associate Professor of Neurosurgery and Pediatrics, University of Pennsylvania School of Medicine

4:05 P.M. **Segmental Neurotransmitters: Role in Nociception**
CHARLES J. HODGE, M.D., Syracuse
Professor of Neurosurgery, State University of New York Upstate Medical Center

4:30 P.M. **CNS (Central Nervous System) Trauma: Thoughts for the Future**
PAUL R. COOPER, M.D., New York City
Associate Professor, Neurosurgery, New York University School of Medicine

(*continued*)

Occupational Medicine
Medical Legal and Workers' Compensation Matters

2:00 P.M.–5:00 P.M.
ROYAL BALLROOM A

CONTINUING MEDICAL EDUCATION CREDIT:
AMA, PRA, 3 Hours, Category 1; AAFP, 2½ Hours, Prescribed

CLINICAL, PREVENTIVE, AND LEGAL ASPECTS OF JOB STRESS

GOTTFRIED F. H. LEHMANN, M.D., Jamaica, *Moderator*

Consultant to Law Department, Division of Workers' Compensation, City of New York; Former Medical Director, Long Island Railroad

Objective: Present information and discuss issues on clinical, preventive and legal aspects of stress and violence at work, which will be of interest and use to physicians practicing in New York State.

2:00 P.M. **Physiologic Stress and Shift Work**

SUZANNE H. RODGERS, Ph.D., Rochester

Consultant in Ergonomics/Human Factors

2:30 P.M. **Employee Assistance/Alcoholism Programs in New York State**

DONALD SANDIN, New York City

President, Donald Sandin & Associates, Inc., Consultants for Employee Assistance/Alcoholism Programs

3:00 P.M. **Coffee Break to View Exhibits**

3:20 P.M. **Clinical Aspects of Stress and Violence at Work**

RICHARD K. ROSS, M.D., Port Washington

Medical Director, Fairchild Republic Corporation, Farmingdale; Associate Medical Director, Executive Health Examiners, New York City

4:00 P.M. **Medical-Legal Aspects of Stress and Violence at Work**

WILLIAM MILLWOOD, J.D., Washington, DC

Senior Vice President and General Counsel, JMW Settlements, Inc.; Former Chief Claims Officer, Southern Railway Corporation

4:30 P.M. **Panel Discussion**

RICHARD E. BOLT, M.D., Rochester

Clinical Instructor, Department of Preventive, Family and Rehabilitation Medicine, University of Rochester School of Medicine and Dentistry; Physician, Eastman Kodak Company

SATURDAY, JUNE 30, 1984

Chest Diseases

9:00 A.M.–12:00 NOON
REGENCY BALLROOM

CONTINUING MEDICAL EDUCATION CREDIT:
AMA, PRA, 3 Hours, Category 1; AAFP, 2½ Hours, Prescribed

THE LUNG AND A HOSTILE ENVIRONMENT

JOHN A. POGGI, M.D., Albany, *Moderator*

Associate Professor of Medicine, Albany Medical College of Union University; Attending Physician, Albany Medical Center Hospital

Objective: The lung's response to a variety of insults will be discussed, updating the physician on the latest diagnostic and therapeutic modalities.

9:00 A.M. **Asbestos: Adding Insult to Injury**

J. RICHARD TYNER, M.D., Albany

Clinical Assistant and Professor of Medicine, Albany Medical College of Union University; Assistant Attending Physician, Pulmonary Division, Albany Medical Center Hospital

9:25 A.M. **Update "AIDS" (Acquired Immune Deficiency Syndrome)**

JAMES P. SMITH, JR., M.D., New York City

Professor of Clinical Medicine, Cornell University Medical College; Director, Respiratory Intensive Care Unit, The New York Hospital

9:50 A.M. **The 33rd Howard Lilienthal Memorial Lecture: Adult Respiratory Distress Syndrome and Trauma**

THOMAS A. NEFF, M.D., Denver, Colorado

Associate Professor of Medicine, University of Colorado Health Science Center; Head, Pulmonary Service, Denver General Hospital

10:50 A.M. **Coffee Break to View Exhibits**

(continued)

11:10 A.M. **Pulmonary Damage from Smoke Inhalation**

FREDERICK R. BEEREL, M.D., Williamsville

Associate Professor of Clinical Medicine, State University of New York at Buffalo School of Medicine

11:35 A.M. **Rapid Diagnosis and Treatment of Chest Trauma—Guidlines**

EMIL A. NACLERIO, M.D., New York City

Clinical Professor of Surgery, New York Medical College; Active Consultant of Thoracic Surgery and Trauma Service, Harlem Hospital of Columbia University College of Physicians and Surgeons

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Obstetrics and Gynecology

9:00 A.M.–1:00 P.M.
VERSAILLES TERRACE

CONTINUING MEDICAL EDUCATION CREDIT:
AMA, PRA, 4 Hours, Category 1; AAFP, 3½ Hours, Prescribed

MENOPAUSE: A TIME OF CHANGE

MURRAY L. NUSBAUM, M.D., Utica, *Moderator*

Clinical Professor, Obstetrics and Gynecology, State University of New York Upstate Medical Center, Syracuse; Medical Director, Ferre Institute

Objective: (1) To review the menopausal changes and explain their causes, (2) to outline the natural course of the menopause and possible associated disease, and (3) to propose a method of treatment.

9:00 A.M. **Introductory Remarks**

MURRAY L. NUSBAUM, M.D., Utica

9:05 A.M. **Understanding the Changes**

SHAWKY BADAWY, M.D., Syracuse

Professor of Obstetrics and Gynecology; Director, Reproductive Endocrinology and Fertility, State University of New York Upstate Medical Center

9:35 A.M. **Discussion**

9:40 A.M. **Neurotransmittors and the Menopause**

FATMA ALEEM, M.D., New York City

Associate Professor of Obstetrics and Gynecology; Director, Endocrine and Infertility Service, New York Medical College

10:10 A.M. **Discussion**

10:15 A.M. **Gynecologic Cancers of Menopause**

THOMAS CAPUTO, M.D., New York City

Professor of Clinical Obstetrics and Gynecology; Director of Gynecological Oncology, New York Hospital—Cornell Medical Center

10:45 A.M. **Discussion**

10:50 A.M. **Coffee Break to View Exhibits**

11:05 A.M. **Sexuality and the Menopause**

LOUISE TYRER, M.D., New York City

Vice President for Medical Affairs, Planned Parenthood Federation of America

11:35 A.M. **Discussion**

11:40 A.M. **Osteoporosis**

ROBERT LINDSAY, Ph.D., West Haverstraw

Director, Regional Bone Center, Helen Hayes Hospital; Professor of Clinical Medicine, Columbia University College of Physicians and Surgeons, New York City

12:10 P.M. **Discussion**

12:15 P.M. **Treatment of the Menopause with Estrogens**

RALPH JEWELEWICZ, M.D., New York City

Associate Professor, Obstetrics and Gynecology, Columbia University College of Physicians and Surgeons

12:45 P.M. **Discussion**

Hand Surgery
Joint Meeting With
The New York Society for Surgery of the Hand

9:00 A.M.–5:00 P.M.
ROYAL BALLROOM B

CONTINUING MEDICAL EDUCATION CREDIT:
AMA, PRA, 7 Hours, Category 1; AAFP, 6½ Hours, Prescribed

UPDATE ON PRIMARY HAND CARE

THOMAS JOSEPH PALMIERI, M.D., New Hyde Park, *Moderator*

Assistant Professor of Clinical Surgery, State University of New York at Stony Brook; Physician-in-Charge, Hand Service, Long Island Jewish-Hillside Medical Center

(continued)

Objective: This course is designed to provide the primary care physicians, orthopedic, plastic, and general surgeons, as well as nurses, therapists, and paramedical personnel with an update on the principles of hand surgery care, including the recognition and diagnosis of various disease entities, and the latest information on the medical and surgical options for treatment, both initial and definitive.

9:00 A.M. **Examination of the Hand**

S. ASHBY GRANTHAM, M.D., New York City

Professor, Clinical Orthopedic Surgery, Columbia University College of Physicians and Surgeons

9:30 A.M. **The Radiologic Evaluation of the Hand**

ALEX NORMAN, M.D., New York City

Director, Deartment of Radiology, Hospital for Joint Diseases, Orthopedic Institute; Professor of Radiology, Mount Sinai School of Medicine of the City University of New York

10:00 A.M. **Principles of Primary Treatment Including the Use of Local Anesthesia**

CLAYTON A. PEIMER, M.D., Buffalo

Associate Professor of Orthopedic Surgery; Chief of Hand Surgery Service, Department of Orthopedic Surgery, Erie County Medical Center

10:30 A.M. **Infections of the Hand**

THOMAS J. PALMIERI, M.D., New Hyde Park

11:00 A.M. **Coffee Break to View Exhibits**

11:15 A.M. **Treatment of Amputated Parts of the Upper Extremity**

BERISH STRAUCH, M.D., The Bronx

Professor and Chief, Division of Plastic Surgery, Albert Einstein College of Medicine of Yeshiva University and Montefiore Hospital and Medical Center

11:45 A.M. **Treatment of Fingertip Injuries**

CHARLES MELONE, JR., M.D., New York City

Clinical Associate Professor of Orthopedic Surgery, New York University Medical Center; Director, Hand Surgery Service, Cabrini Medical Center

12:15 P.M. **Tendon Injuries**

ROBERT SCHULTZ, M.D., Valhalla

Professor and Chairman, Department of Orthopedics and Director, Sylvester Carter Hand Service, New York Medical College; Director of Orthopedic Surgery, Westchester Medical Center

1:00 P.M. **Lunch**

2:00 P.M.–5:00 P.M.

2:00 P.M. **Nerve Entrapment Syndromes in the Upper Extremity**

MARTIN POSNER, M.D., New York City

Associate Clinical Professor of Orthopedic Surgery, Mount Sinai School of Medicine of the City University of New York; Chief, Hand Service, Mount Sinai Hospital, Lenox Hill Hospital, and Hospital for Joint Diseases, Orthopedic Institute

2:30 P.M. **Common Hand Tumors**

HAROLD DICK, M.D., New York City

Clinical Professor of Orthopedic Surgery, Columbia University College of Physicians and Surgeons

3:00 P.M. **Tenosynovitis of the Hand and Wrist**

STEVEN GREEN, M.D., New York City

Associate Attending, Hospital for Joint Diseases, Orthopedic Institute; Assistant Clinical Professor of Orthopedic Surgery, Mount Sinai School of Medicine of the City University of New York

3:30 P.M. **Coffee Break to View Exhibits**

3:45 P.M. **Joint and Ligament Problems: Sprains and Dislocations**

RICHARD EATON, M.D., New York City

Associate Professor of Surgery, Columbia University College of Physicians and Surgeons

4:15 P.M. **Hand and Wrist Fractures**

RONALD MATCH, M.D., Glen Cove
Hand Surgeon, Community Hospital of Glen Cove;
Assistant Professor of Surgery,
State University of New York at Stony Brook

4:45 P.M. **Question and Answer Period**

Internal Medicine

9:00 A.M.–5:00 P.M.
GEORGIAN BALLROOM A

CONTINUING MEDICAL EDUCATION CREDIT:
AMA, PRA, 6 Hours, Category 1; AAFP, 5 Hours, Prescribed

ADVANCES IN BIOMEDICAL ENGINEERING: CLINICAL APPLICATIONS

SIDNEY S. WEINSTEIN, M.D., Rochester, *Moderator*

Clinical Associate Professor of Medicine, University of Rochester School of Medicine and Dentistry

Objective: To acquaint physicians with the clinical use of new technology that has recently or will soon become available for general use.

(*continued*)

(SATURDAY continued)

9:00 A.M. **Recombinant Technology and Treatment of Diabetes Mellitus: Triumph, Question, Promise**

John Galloway, M.D., Indianapolis, Indiana

Senior Clinical Pharmacologist, Lilly Laboratory for Clinical Research; Professor of Medicine, Indiana University School of Medicine

9:50 A.M. **Insulin Pump Treatment of Type I Diabetes Mellitus**

William Tamborlane, M.D., New Haven, Connecticut

Associate Professor of Pediatrics, Yale University School of Medicine

10:30 A.M. **Coffee Break to View Exhibits**

11:00 A.M. **Therapeutic Plasmapheresis**

Jacob Nusbacher, M.D., Pittsburgh, Pennsylvania

Medical Director, Central Blood Bank of Pittsburgh; Professor of Medicine and Pathology, University of Pittsburgh School of Medicine

11:40 A.M. **Clinical Use of Implantable Defibrillators**

Arthur Moss, M.D., Rochester

Clinical Professor of Medicine, University of Rochester School of Medicine and Dentistry

2:00 P.M.–5:00 P.M.

Paul J. Rosch, M.D., Yonkers, *Moderator*

Clinical Professor of Medicine, New York Medical College; President, American Institute of Stress

2:00 P.M. **Lasers and Other Mechanical Devices in the Treatment of Cancer Patients**

Harvey Lerner, M.D., Philadelphia, Pennsylvania

Head, Section of Surgical Oncology and Cancer Chemotherapy, Pennsylvania Hospital

2:50 P.M. **Nuclear Magnetic Resonance**

Gordon Potts, M.D., New York City

Professor of Radiology, Cornell University Medical College

3:30 P.M. **Coffee Break to View Exhibits**

3:50 P.M. **Digital Subtraction Angiography**

Michael Deck, M.D., New York City

Professor of Clinical Radiology, Cornell University Medical College

4:30 P.M. **Ultrasound for the 80s**

Raymond Gramiak, M.D., Rochester

Professor of Radiology, University of Rochester School of Medicine and Dentistry

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Ophthalmology

9:00 A.M.–5:00 P.M.
ROYAL BALLROOM A

CONTINUING MEDICAL EDUCATION CREDIT:
AMA, PRA, 6½ Hours, Category 1; AAFP, 5 Hours, Prescribed

DISEASES AND TRAUMA OF THE ORBIT AND LIDS

Paul J. Loree, M.D., Tonawanda, *Moderator*

Instructor of Surgery (Ophthalmology) State University of New York at Buffalo; Director, New York State Ophthalmological Society

Objective: To inform audience of latest development in techniques of diagnosis and treatment of lid and orbital disease.

9:10 A.M. **The Analogy of the Pathophysiology and Surgery of Involutional Ptosis and Involutional Entropion**

Arthur J. Schaefer, M.D., Snyder

Associate Clinical Professor of Ophthalmology, State University of New York at Buffalo; Chief of Ophthalmic Plastic and Reconstructive Surgery, Erie County Medical Center and Buffalo General Hospital

9:55 A.M. **The Diagnosis and Treatment of Orbital Fractures**

Byron Smith, M.D., New York City

Clinical Professor of Ophthalmology, New York Medical College; Consultant in Ophthalmic Plastic Surgery, New York Eye and Ear Infirmary and the Manhattan Eye, Ear and Throat Hospital

10:40 A.M. **Coffee Break to View Exhibits**

11:00 A.M. **The Diagnosis of Treatment of Lid Tumors**

Stephen L. Bosniak, M.D., New York City

Associate Adjunct Surgeon, Department of Ophthalmic Plastic and Reconstructive Surgery, New York Eye and Ear Infirmary; Assistant Attending Surgeon, Department of Ophthalmic Plastic and Reconstructive Surgery, Manhattan Eye, Ear and Throat Hospital

11:45 A.M. **Questions and Answers**

12:30 P.M. **Lunch**

2:00 P.M.–5:00 P.M.

2:00 P.M. **Management of Lid and Canthal Trauma: Cosmetic Blepharoplasty**

Robert C. Della Rocca, M.D., New York City

Surgeon Director, Oculoplastic and Orbital Service, New York Eye and Ear Infirmary; Attending, Montefiore Hospital and Medical Center, The Bronx

2:45 P.M. **Trauma in the Orbital Region**

John Thayer Simonton, M.D., Rye

Clinical Professor of Ophthalmology, New York University School of Medicine, New York City; Chief of Oculoplastic Service, New York Eye and Ear Infirmary, New York City

(continued)

(SATURDAY continued)

3:30 P.M. **Coffee Break to View Exhibits**

3:50 P.M. **Eyelid Reconstruction**

ORKAN GEORGE STASIOR, M.D., Albany

Clinical Professor of Ophthalmology,
Albany Medical College of Union University;
Director, of Oculoplastic Service,
the Albany Medical Center Hospital

4:35 P.M. **Questions and Answers**

GENERAL SESSION

9:00 A.M.–5:00 P.M.
GEORGIAN BALLROOM B

CONTINUING MEDICAL EDUCATION CREDIT:
AMA, PRA, 6 Hours, Category 1; AAFP, 5 Hours, Prescribed

VIOLENCE

Objective: Following the theme of this 1984 Assembly, this portion of the program will acquaint physicians with several areas where the violence and terrorism of this latter half of the 20th century impact on the practice of medicine. It is proposed to alert physicians to various patterns of behavior and how they should be handled. Discussion will cover the social, psychiatric and medical implications of this violent culture.

9:00 A.M. **Introduction**

STEPHEN NORDLICHT, M.D., New York City

Chairman, Scientific Program Committee, Medical Society of the State of New York; Consulting Psychiatrist, the Police Department of the City of New York

9:05 A.M. **Introduction and Opening Remarks**

ALAN BLUM, M.D., Lake Success, *Moderator*

Editor, New York State Journal of Medicine; Director, Division of Scientific Publications, Medical Society of the State of New York

9:10 A.M. **Violence on the Highway: A National Public Health Problem**

JOHN D. STATES, M.D., Rochester

Chairman and Professor, Department of Orthopedics, University of Rochester School of Medicine and Dentistry; Chairman, Accident and Injury Prevention Committee, Medical Society of the State of New York

9:30 A.M. **Violence in Sports**

WILLIBALD NAGLER, M.D., New York City

Jerome and Anne Fischer Physiatrist-in-Chief, New York Hospital—Cornell Medical Center

9:50 A.M. **Sexual Abuse of Children**

MARVIN L. BLUMBERG, M.D., Jamaica

Chairman, Department of Pediatrics, The Jamaica Hospital; Chairman, Child Abuse Committee, Medical Society of the State of New York

10:10 A.M. **Questions and Discussion**

10:30 A.M. **Coffee Break to View Exhibits**

10:45 A.M. **Patterns of Drug Abuse in Adolescents**

RONALD J. DOUGHERTY, M.D., Syracuse

Administrative Service Chief, Chemical Abuse Recovery Service, Benjamin Rush Center; Chairman, Drug Abuse Committee, Medical Society of the State of New York

11:05 A.M. **Violence in Institutions**

STEVEN E. KATZ, M.D., Albany

Commissioner of Mental Health, New York State

11:25 A.M. **Violence and the Law**

ARCHIBALD R. MURRAY, L.L.B., New York City

Executive Director and Attorney-in-Chief of the Legal Aid Society

11:45 A.M. **Questions and Discussion**

12:00 Noon **Luncheon and Viewing Exhibits**

2:00 P.M.–5:00 P.M.

DAVID R. MCNUTT, M.D., New York City, *Moderator*

Director, The New York Academy of Medicine

2:10 P.M. **Violence and the Third World**

Sister HELENE O'SULLIVAN, M.M., Maryknoll

Director, Office of Social Concerns of the Maryknoll Sisters

2:30 P.M. **Wounds of War**

WILLIAM D. SHARPE, M.D., New York City

Director, Department of Pathology, Cabrini Medical Center

2:50 P.M. **The Police Perspective of Violence**

Mr. PATRICK V. MURPHY, Washington, D.C.

President, Police Foundation

3:10 P.M. **Questions and Discussion**

3:30 P.M. **Coffee Break to View Exhibits**

3:45 P.M. **The Medical Consequences of Nuclear Warfare**

GEORGE G. READER, M.D., New York City

Professor and Chairman, Department of Public Health, The New York Hospital—Cornell Medical Center

(continued)

4:05 P.M. **The Psychiatric Aspects of Terrorism**

STEPHEN NORDLICHT, M.D., New York City

Consulting Psychiatrist, Memorial Sloan-Kettering Cancer Center, Cornell University Medical College

4:25 P.M. **The Realism of Peace**

Rev. DONALD W. SHRIVER, Ph.D., New York City

President of the Union Theological Seminary in the City of New York

4:45 P.M. **Questions and Discussion**

Pathology
Gastroenterology and Colon and Rectal Surgery

1:30 P.M.–5:00 P.M.
REGENCY BALLROOM

CONTINUING MEDICAL EDUCATION CREDIT:
AMA, PRA, 3½ Hours, Category 1; AAFP, 3 Hours, Prescribed

ENDOSCOPIC BIOPSY IN GASTROINTESTINAL DISEASES

PRIMITIVO T. CRUZ, M.D., Norwich, *Moderator*

Pathologist and Director of Laboratories, Chenango Memorial Hospital, and Community Memorial Hospital, Hamilton; Assistant Clinical Professor in Pathology, State University of New York Upstate Medical Center

Objective: Our objectives are to correlate endoscopic biopsy findings with clinical diagnosis of common gastrointestinal problems and to familiarize physicians with the endoscopic findings in AIDS (Acquired Immune Deficiency Syndrome).

1:30 P.M. **ANDRESEN MEMORIAL LECTURE: Endoscopic Biopsies, Pathological Considerations**

HEIDRUN ROTTERDAM, M.D., New York City

Attending pathologist, Lenox Hill Hospital; Assistant Clinical Professor of Pathology, Columbia University College of Physicians and Surgeons

2:35 P.M. **Discussion**

3:05 P.M. **Coffee Break to View Exhibits**

3:25 P.M. **Endoscopic Biopsies, Clinical Considerations**

MYRON GOLDBERG, M.D., New York City

Associate Attending Physician, Lenox Hill Hospital; Assistant Clinical Professor of Medicine, New York Medical College

4:30 P.M. **Discussion**

Dermatology and Syphilogy
Otolaryngology—Head and Neck Surgery

2:00 P.M.–5:00 P.M.
VERSAILLES TERRACE

CONTINUING MEDICAL EDUCATION CREDIT:
AMA, PRA, 3 Hours Category 1; AAFP, 2½ Hours, Prescribed

CUTANEOUS MALIGNANCIES AND THEIR TREATMENT

FRANKLIN S. GLICKMAN, M.D., Brooklyn, *Moderator*

Clinical Professor of Dermatology, State University of New York Downstate Medical Center; Chairman, Section on Dermatology and Syphilology, Medical Society of the State of New York

STEVEN M. PARNES, M.D., Albany, *Moderator*

Acting Head, Otolaryngology, Albany Medical College of Union University; Chairman, Section on Otolaryngology—Head and Neck Surgery, Medical Society of the State of New York

Objective: The program is designed to acquaint the physician with select dermatologic problems of the head and neck area using a multidisciplinary approach.

2:00 P.M. **Ultra-Violet Carcinogenesis: Immunologic Aspects**

NEIL BRODY, Ph.D., Brooklyn

Associate Professor and Vice Chairman, Department of Dermatology, State University of New York Downstate Medical Center

2:30 P.M. **Melanoma Update**

ALFRED W. KOPF, M.D., New York City

Professor of Dermatology, Skin and Cancer Unit, New York University School of Medicine

(*continued*)

3:00 P.M. **Evaluation and Management of Malignant Skin Lesions**

KENNETH SKOLNICK, M.D., Sewickley, Pennsylvania

Assistant Clinical Professor of Otolaryngology—Head and Neck Surgery, University of Pittsburgh School of Medicine

3:30 P.M. **Coffee Break to View Exhibits**

3:50 P.M. **Management of Soft Tissue Trauma**

JEROME C. GOLDSTEIN, M.D., Washington, D.C.

Executive Vice President, American Academy of Otolaryngology—Head and Neck Surgery

4:25 P.M. **Basal and Squamous Cell Carcinoma: Alternatives to Excisional Surgery**

LASZLO BIRO, M.D., Brooklyn

Clinical Professor of Dermatology, State University of New York Downstate Medical Center

SUNDAY, JULY 1, 1984

Allergy and Immunology

9:00 A.M.–1:00 P.M.
GEORGIAN BALLROOM A

CONTINUING MEDICAL EDUCATION CREDIT: AMA, PRA, 4 Hours, Category 1; AAFP, 3½ Hours, Prescribed

ALLERGY AND IMMUNOLOGY UPDATE

ANDRE J. CODISPOTI, M.D., Suffern, *Moderator*

Attending, Department of Allergy & Immunology, Long Island College Hospital, Brooklyn; Attending, Subsection Allergy, Department of Pediatrics, Good Samaritan Hospital

Objective: The objective of the program will be to present both to the specialist and primary care physician, the latest information in five major areas of allergy and immunology.

9:10 A.M. **Bronchial Asthma**

LAWRENCE T. CHIARAMONTE, M.D., Brooklyn

Director, Department of Allergy & Immunology, The Long Island College Hospital; Clinical Assistant Professor, State University of New York Downstate Medical Center

9:45 A.M. **Immunoregulation**

EUGENIA HAWRYLKO, M.D., Brooklyn

Chief, Immunology Laboratory, The Long Island College Hospital; Instructor of Clinical Medicine, Department of Medicine, New York University Medical Center

10:30 A.M. **Coffee Break to View Exhibits**

10:50 A.M. **Food Allergy**

ARLENE SCHNEIDER, M.D., Brooklyn

Associate Director, Department of Allergy and Immunology, The Long Island College Hospital; Clinical Assistant Professor, State University of New York Downstate Medical Center

11:20 A.M. **Allergic Rhinitis**

GUY A. SETTIPANE, M.D., Providence, Rhode Island

Director, Division of Allergy, Department of Medicine, Rhode Island Hospital; Associate Clinical Professor of Medicine, Brown University

11:55 A.M. **A.I.D.S. (Acquired Immune Deficiency Syndrome)**

MICHAEL H. GRIECO, M.D., New York City

Director, R. A. Cook Institute of Allergy, St. Luke's-Roosevelt Hospital Center; Professor of Clinical Medicine, Columbia University College of Physicians and Surgeons

12:30 P.M. **Panel Discussion**

(continued)

GENERAL SESSION
Emergency Medicine/Urology
Radiology

9:00 A.M.–1:00 P.M.
ROYAL BALLROOM A

CONTINUING MEDICAL EDUCATION CREDIT:
AMA, PRA, 4 Hours, Category 1; AAFP, 3½ Hours, Prescribed

VIOLENCE AND GU (GENITOURINARY) TRAUMA

TAMARATH K. YOLLES, M.D., Stony Brook, *Moderator*

Professor of Community Medicine; Associate Dean for Continuing Medical Education, State University of New York at Stony Brook; Chairman, Section on Emergency Medicine, Medical Society of the State of New York

and

IRWIN FRANK, M.D., Rochester, *Moderator*

Professor of Urology, University of Rochester School of Medicine & Dentistry; Chairman, Section on Urology, Medical Society of the State of New York

Objective: To define the approach to the patient with GU (Genitourinary) Trauma; to elucidate the pitfalls and cautions in sequencing studies and positioning the patient for radiologic studies; to demonstrate a schema for study in a patient with a presenting sign (hematuria); to define the problems in diagnosis and management in injuries to the various parts of the GU system.

9:00 A.M. **Priorities in the Management of Urologic Trauma**

WAYNE LONGMORE, M.D., New York City

Attending Physician, Bellevue Hospital Center; Clinical Instructor, Department of Surgery, New York University School of Medicine

9:25 A.M. **Radiology of Urologic Trauma**

HOWARD BERMAN, M.D., Valhalla

Associate Professor of Radiology, Department of Radiology, Westchester County Medical Center

9:50 A.M. **Hematuria: What Do We Do Now**

JEFFREY MARGULIES, M.D., Stony Brook

Director of Emergency Services, University Hospital; Assistant Professor of Medicine, State University of New York at Stony Brook

10:15 A.M. **The Physiology of Trauma**

WILLIAM STAHL, M.D., Valhalla

Associate Professor of Surgery, New York Medical College

10:40 A.M. **Coffee Break to View Exhibits**

11:00 A.M. **Renal Trauma**

SALAH AL-ASKARI, M.D., New York City

Professor of Urology, New York University School of Medicine

11:30 A.M. **Bladder Trauma**

JOSEPH ADDONIZIO, M.D., Valhalla

Professor and Chairman, Department of Urology, New York Medical College

12:00 NOON **Urethral Injuries**

RICHARD MACCHIA, M.D., Brooklyn

Acting Chairman, Department of Urology, State University of New York Downstate Medical Center

12:30 P.M. **Scrotal Injuries**

ANN HARWOOD, M.D., Jacksonville, Florida

Assistant Professor of Surgery; Chairman of Emergency Medicine, University Hospital

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ANNUAL MEETING
Women's Medical Society of New York State
Joint Meeting With
American Medical Women's Association Branch 18

9:00 A.M.–1:00 P.M.
VERSAILLES TERRACE

CONTINUING MEDICAL EDUCATION CREDIT:
AMA, PRA, 4 Hours, Category 1; AAFP, 3¾ Hours, Prescribed

WOMEN'S HEALTH ISSUES AND FEMALE PHYSICIANS

JEANNE SMITH, M.D., New York City, *Moderator*

Faculty, American Institute for Psychoanalysis; Chairperson, Women's Medical Society of New York State

Objective: Many women today are becoming more and more dependent, and insistent upon, female physicians for their medical needs. Today's program will attempt to cover areas of medical care where the relationship between female patient and female physician may be very significant.

(*continued*)

(SUNDAY continued)

9:00 A.M. **Recent Developments in Self Blood Glucose Monitoring by the Pregnant Diabetic**

Lois Jovanovic, M.D., New York City

Assistant Professor of Medicine, The New York Hospital—Cornell Medical Center

9:20 A.M. **Medical and Ethical Dilemmas in Drug Therapy with Psychiatric Patients**

Margaret Madden, M.D., New Britain, Connecticut

Senior Psychiatrist, Outpatient Department, Connecticut Valley Hospital

9:50 A.M. **Advances in Pediatric Cardiology**

Mary Ellen Engle, M.D., New York City

Stavros S. Niarchos Professor of Pediatric Cardiology; Professor of Pediatrics and Director of Pediatric Cardiology, The New York Hospital—Cornell Medical Center

10:30 A.M. **Coffee Break to View Exhibits**

10:45 A.M. **Controversies in Management of Menopause**

Lila A. Wallis, M.D., New York City

Associate Clinical Professor of Medicine, Cornell University Medical College

11:35 A.M. **Violence Against Women: The Myth of Masochism**

Alexandra Symonds, M.D., New York City

Associate Clinical Professor of Psychiatry, New York University School of Medicine

12:30 P.M. **Question and Answer Period**

GENERAL SESSION

Family Practice/Preventive Medicine/Psychiatry

9:00 A.M.–5:00 P.M.
ROYAL BALLROOM B

CONTINUING MEDICAL EDUCATION CREDIT: AMA, PRA, 7 Hours; Category 1; AAFP, 6 Hours, Prescribed

LIVING WITH VIOLENCE

Willard C. Schmidt, M.D., Ithaca, *Moderator*

Health Commissioner, Tompkins County; Consultant in Infectious Disease, Preventive Medicine, and Public Health, Tompkins Community Hospital

Objective: To illustrate some of the medical consequences of socio-economic problems in community life and the prevention, management and treatment of these problems.

9:10 A.M. **The High Risk Infant: Socio-Environmental Factors Contributing to Aetiology and Prognosis**

Henry N. Ricciuti, Ph.D., Ithaca

Professor and Chairman, Department of Human Development and Family Studies, Cornell University Medical College

9:45 A.M. **Discussion**

10:00 A.M. **Urban Teenagers: A Lost Generation**

Eric A Schaff, M.D., Rochester

Instructor, Department of Preventive Medicine, Family Medicine, and Rehabilitation, University of Rochester School of Medicine and Dentistry

10:35 A.M. **Discussion**

10:50 A.M. **Coffee Break to View Exhibits**

11:10 A.M. **Assessment of Sexually Assaulted Females**

Ronald V. Uva, M.D., Oswego

Clinical Instructor, State University of New York Upstate Medical Center, Syracuse; Attending Physician, Oswego Hospital

11:45 A.M. **Discussion**

12:00 NOON **Women, Stress, and Medication**

Ms. Joan Levine, Buffalo

Director, Womanfocus

12:35 P.M. **Discussion**

2:00 P.M.–5:00 P.M.

2:00 P.M. **Leonard Kane, M.D., Brooklyn,** ***Moderator***
Unit Chief, In-Patient Psychiatry, Interfaith Medical Center

2:05 P.M. **Prescription and Non-Prescription Drug Abuse**

Ronald Dougherty, M.D., Brewerton

Chairman, Committee on Drug Abuse, Medical Society of the State of New York; Medical Director and President, Pelion Incorporated

2:45 P.M. **Discussion**

3:00 P.M. **Prospectives on Violence: A Critical Overview of a Human Dilemma**

Richard Drooz, M.D., New York City

Associate Professor, Psychiatry, State University of New York Downstate Medical Center; Private Practice

3:35 P.M. **Discussion**

3:50 P.M. **Coffee Break to View Exhibits**

4:10 P.M. **Adam Berwid and the Obligation to Assess Dangerousness**

Daniel W. Schwartz, M.D., Cedarhurst

Director, Forensic Psychiatry, Kings County Hospital Center, Brooklyn; Associate Professor, Psychiatry, State University of New York Downstate Medical Center

4:45 P.M. **Discussion**

(continued)

GENERAL SESSION
Orthopedic Surgery/General Surgery/Plastic Surgery Rehabilitation Medicine/Anesthesiology

9:00 A.M.-5:00 P.M.
GEORGIAN BALLROOM B

CONTINUING MEDICAL EDUCATION CREDIT:
AMA, PRA, 7 Hours, Category 1; AAFP, 6½ Hours Prescribed

TRAUMA MANAGEMENT: AN UPDATE ON CURRENT TECHNIQUES

Objective: To inform on current advances in the management of the traumatized patient, emphasizing both new techniques and the importance of interdisciplinary approach.

9:00 A.M.-10:55 A.M.—HEAD TRAUMA AND SPINAL INJURIES

Catalino Daroy, M.D., Schenectady, *Moderator*

Attending Psychiatrist, Sunnyview Hospital Rehabilitation Center

9:00 A.M. **Rehabilitation of the Patient with Head Injury**

Arun K. Bhattacharyya, M.D., West Haverstraw

Director of Rehabilitation Medicine, Helen Hayes Hospital

9:25 A.M. **Anesthesia Problems in Spinal Cord Injury**

Joseph P. Griffin, M.D., Brooklyn

Assistant Professor of Anesthesiology, State University of New York Downstate Medical Center

9:50 A.M. **Recent Approaches to the Diagnosis and Management of the Unstable Spine Fracture**

Patrick F. O'Leary, M.D., New York City

Chief, Spine Section, Lenox Hill Hospital

10:15 A.M. **The Spinal Cord Injured Patient**

Kristjan T. Ragnarsson, M.D., New York City

Associate Professor of Rehabilitation Medicine, New York University Medical Center—Institute of Rehabilitation Medicine

10:40 A.M. **Question and Answer Period**

10:55 A.M. **Coffee Break to View Exhibits**

11:15 A.M.-1:00 P.M.—PELVIC AND LOWER EXTREMITIES INJURIES

George Wantz, M.D., New York City, *Moderator*

Attending Surgeon, New York Hospital; Associate Professor, Clinical Surgery, Cornell University Medical College

11:15 A.M. **Vascular Injuries to the Abdomen and Pelvis**

Malcolm D. Perry, M.D., New York City

Professor of Surgery, Cornell University Medical College; Chief, Division of Vascular Surgery, New York Hospital—Cornell Medical Center

11:35 A.M. **Stabilization and Reconstruction of the Acute Pelvic Fracture**

Arthur Sadler, M.D., The Bronx

Associate Professor, Department of Orthopedic Surgery, Albert Einstein College of Medicine of Yeshiva University

11:55 A.M. **Current Orthopedic Approach to Polytraumatized Patient with Multiple Limb Fractures**

Neil Cobelli, M.D., The Bronx

Instructor, Department of Orthopedic Surgery, Albert Einstein College Hospital

12:15 P.M. **Late Sequelae of the Fractured Hip**

David M. Hirsh, M.D., The Bronx

Associate Clinical Professor, Department of Orthopedic Surgery, Albert Einstein College of Medicine of Yeshiva University

12:35 P.M. **Question and Answer Period**

2:00 P.M.-5:00 P.M.

2:00 P.M.-3:15 P.M.—INJURY TO THE LIMBS

David M. Hirsh, M.D., The Bronx, *Moderator*

2:00 P.M. **Gunshot Wounds**

Kenneth Swan, M.D., Newark, New Jersey

Professor of Surgery, New Jersey Medical School, College of Medicine and Dentistry of New Jersey

2:20 P.M. **Traumatic Neuropathies Associated with Orthopedic Injuries**

Ralph Lusskin, New York City

Professor of Clinical Orthopedic Surgery, New York University School of Medicine

2:40 P.M. **The Use of Vascularized Bone Flaps in Acute and Chronic Segmental Bone Loss**

Berish Strauch, M.D., The Bronx

Professor and Chief, Plastic Surgery Division, Albert Einstein College of Medicine and Montefiore Medical Center

3:00 P.M. **Question and Answer Period**

3:15 P.M. **Coffee Break to View Exhibits**

3:30 P.M.-5:00 P.M.—ROLE OF THE PLASTIC SURGEON IN THE CARE OF THE TRAUMATIZED PATIENT

Robert W. Bernard, M.D., White Plains, *Moderator*

Chief of Plastic Surgery, White Plains Hospital

3:30 P.M. **Recent Advances in the Management of Maxillofacial Injuries**

(continued)

BARRY ZEID, M.D., New York City

Assistant Professor of Plastic Surgery, New York University Medical Center

3:50 P.M. **Orbital and Periorbital Trauma**

GLEN JELKS, M.D., New York City

Assistant Professor of Plastic Surgery, New York University Medical Center

4:10 P.M. **The Treatment of Nerve Injuries**

WILLIAM SHAW, M.D., New York City

Chief, Plastic Surgery Service, Bellevue Hospital Center; Director Micro Surgery and Replantation Surgery Service, New York University Medical Center and Bellevue Hospital Center

4:30 P.M. **Early and Late Treatment of Facial Burns**

EDWARD W. POWERS, III, M.D., White Plains

Instructor, Plastic Surgery and Dermatology, New York Hospital—Cornell Medical Center

4:50 P.M. **Question and Answer Period**

Committee on Alcoholism
Joint Meeting With
American Medical Society on Alcoholism, New York State Chapter

2:00 P.M.-5:00 P.M.
ROYAL BALLROOM A

CONTINUING MEDICAL EDUCATION CREDIT:
AMA, PRA, 3 Hours, Category 1; AAFP, 2½ hours, Prescribed

VIOLENCE: CAN THE DOCTOR PREVENT IT

ANNE GELLER, M.D., New York City, *Moderator*

Director, Smithers Alcoholism Treatment Center, St. Luke's—Roosevelt Hospital Center

Objective: Evaluate those aspects of violence that interface with the practice of medicine and offer the physician preventive and therapeutic techniques for dealing with it.

2:00 P.M. **The Faces of Violence: I. The Family**

GEANINE FERRIS PIRRO, Esq., White Plains

Assistant District Attorney, Westchester County; Chief, Domestic Violence Prosecution Bureau

2:30 P.M. **The Faces of Violence: II. The Courts**

Honorable JEROME HORNBLASS, New York City

Judge, Supreme Court, State of New York

3:00 P.M. **The Faces of Violence: III. The Hospital Emergency Rooms**

CANUTE C. BERNARD, M.D., New York City

Attending Surgeon, Harlem Hospital Center

3:30 P.M. **Coffee Break to View Exhibits**

3:50 P.M. **Preventing Violence: The Alcohol Connection**

SHEILA BLUME, M.D., Sayville

Psychiatrist; Former Director, New York State Division of Alcoholism; Former Medical Director, National Council on Alcoholism

4:10 P.M. **How Can the Emergency Room Physician Treat and Prevent Violence**

NORMAN WETTERAU, M.D., Dansville

Family Physician, Nicholas H. Noyes Memorial Hospital

4:30 P.M. **Violence and Its Prevention**
Panel Discussion: The Above Speakers

STANLEY GITLOW, M.D., New York City, *Moderator*

Clinical Professor of Medicine, Mt. Sinai School of Medicine of the City University of New York; Chairman, Committee on Alcoholism, Medical Society of the State of New York

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1984 ANNUAL CME ASSEMBLY

SCIENTIFIC EXHIBITS

EXHIBITION CENTRE
SHERATON CENTRE HOTEL

Hofstra University Health Dome.
Gary Witkin, Ph.D., Executive Director, Hofstra University Health Dome, Hempstead, N.Y.

Hofstra Health Dome's protein-sparing supplemented fasting program, cardiac rehabilitation, and nutrition program will be presented on an 11½ minute audio-visual videotape. An explanation of the programs and investigative studies will also be presented on a slide carousel. Biofeedback demonstration will be available to illustrate how it works and what problems are treated. (Booth 200)

■

Disability Evaluation Under Social Security.
Harry R. Pace, M.D., Chief Medical Consultant, N.Y.S. Dept. of Social Services, New York City

DESCRIPTION: The New York State Office of Disability Determinations is responsible for adjudicating disability applications for claimants residing throughout New York State, under the provisions of the Social Security Act. The Social Security Law defines disability as inability to work because of a medically determinable physical or mental impairment that is expected to result in death or that has lasted or is expected to last at least 12 months. (Booth 201)

■

Malignant Melanoma of the Lower Extremities: Effect of elective lymph nodes Dissection for clinical stage I Melanoma.
Irving M. Ariel, M.D., P.C., The Pack Foundation & the Cabrini Medical Center, New York City

DESCRIPTION: The value of elective groin dissection in melanoma patients. (Booth 202)

■

Rotary Instability of the Knee-Reconstruction of the Anterior Cruciate and Medial and Lateral Elements with Fascia Lata Substitution.
Joseph F. Giattini, M.D., Chief of Service, New York Medical College, New York City

DESCRIPTION: A demonstration of fascia lata reconstruction of knee ligaments including the postero-lateral, postero-medial corners and the anterior cruciate. (Booth 203)

■

Cryosurgery of Benign and Malignant Skin Tumors.
Laszlo Biro, M.D., F.A.C.P.,—Clinical Professor of Dermatology, SUNY, Brooklyn, N.Y.

DESCRIPTION: The exhibit will demonstrate the use of cryosurgery in the management of benign and malignant skin tumors. Photographs will illustrate before and after treatment. Usefulness of cryosurgery will be especially stressed in the pediatric and geriatric age groups. A video-tape prepared by the Network of Continuing Medical Education will demonstrate the technique of office cryosurgery. (Booth 204)

■

Monochromatic Light Ophthalmoscopy.
Louis Antonucci, M.D., Chief Retinal Service, Erie County Medical Center, Buffalo, New York

The exhibit depics the use of monochromatic light in aiding in the diagnosis of various diseases of the Retina using the Ophthalmoscope. (Booth 205)

■

Rehabilitation of Bilateral Above Knee Amputee.
Jacob Nir, M.D., Resident, Kingsbrook Jewish Medical Center, Brooklyn, New York

Rehabilitation of the elderly above-knee double amputee. J. Nir, I. Osnis, V. Naughton, A. P. Ruskin.

The elderly above-knee double amputee is almost always considered unsuitable for prosthetic rehabilitation and is relegated to a wheelchair existence. Historically, younger individuals have been provided with "stubbies" and only rarely has prosthetic rehabilitation been attempted. We present the case of a 76-year-old man amputated secondary to peripheral vascular disease. Successful prosthetic rehabilitation was achieved in this individual with a specially designed shortened prosthesis which reduced his body height by six inches and provided him with a stable base for ambulation requiring a low level of energy. Aspects of biomechanical gait analysis, as well as work physiology studies and energy consumption are discussed, showing the advantages and feasibility of this approach for the elderly patient. The psychologic implications of reduction in body height will also be presented. (Booth 206)

■

Simultaneous Bilateral Carotid Endarterectomies.
Roy H. Clauss, M.D., Professor of Surgery, New York Medical College, Valhalla, N.Y.

DESCRIPTION: Operative and post operative complication of simultaneous bilateral carotid endarterectomies performed in 37 patients compared favorably with those observed in 100 patients having unilateral operations.
The physiological basis, clinical rationale, and actual advantages of operating upon both carotid arteries during one anesthesia are portrayed. (Booth 207)

■

Intraoperative Anticoagulation During Arterial Reconstructive Procedures.
Bok Y. Lee, M.D., Chief, Surgical Service, Veterans Administration Medical Center Castle Point, N.Y.

DESCRIPTION: The Intraoperative administration of Calciparin (70 μ/kg) produces widely variant interpatient responses as monitored by thromboelastography (TEG). Using TEG, there was no need for the use of protamine to reverse the effect of heparin and there were no hemorrhagic complications. Hypersensitivity to heparin was noted in 2 patients, hyposensitivity in 1 patient and unusual consumption (need for additional heparin during first 2 hours of operation) was noted in 5 patients. TEG appears to be a useful method of monitoring heparin administration during vascular surgical procedures. (Booth 208)

■

A Creative Approach for Educating Hospital Personnel.
Linda Chiarello, B.S., R.N.,—Infection Control Coordinator. Mary Imogene Bassett Hospital, Cooperstown, N.Y.

DESCRIPTION: The exhibit displays a representative sample of subjects presented as a Poster Session as part of an Infection Control Teaching Day. It demonstrates an innovative approach toward teaching hospital staff and has had a particular appeal among physicians. (Booth 209)

Caustic Injuries of the Esophagus. Diagnosis and Management.

Luis E. Cortes, M.D., Assistant Professor of Surgery, New York Medical College, Valhalla, N.Y.

DESCRIPTION: Caustic injuries of the esophagus are very difficult management problems. A classification of caustic injuries and indications for different types of treatment are displayed. A detailed description of the esophageal stent used for severe burns of the esophagus is demonstrated. Excellent clinical results with 4 year follow up are presented. (Booth 210)

■

Thermography, Tissue Compliance and Pressure Threshold in Objective Evaluation of Soft Tissue Injuries

Andrew A. Fischer, M.D., Ph.D., Chief, Rehab. Medicine Service, Bronx VAMC, N.Y.

DESCRIPTION: Thermography (non invasive heat Imaging by infrared or liquid crystal technique) is useful for documentation of pain and diagnosis of its origin. Disc disease, radiculopathy, soft tissue injuries, myofascial pain, circulatory disorders can be diagnosed and visualized for clinical use or medico-legal documentation. Tissue compliance is a new technique for recording objectively muscle spasm. Pressure threshold quantifies local tenderness and aids so in documentation of trigger points. (Booth 211)

■

Lacrimal Surgical Techniques.

Pierre Guibor, M.D., Director, Oculoplastic Service, New York Medical College, Valhalla, N.Y.

DESCRIPTION: This exhibit emphasizes specific surgical techniques in the use of dacryo-cystorhinostomy and canalicular reconstruction with the canalicular intubation set. Lacrimal reconstruction following trauma, as well as nasal fractures, will be exemplified with video modalities. (Booth 212)

■

Computerized Tomography of the Temporomandibular Joint.

William E. Mattey, M.D., Chairman of Dept. of Radiology, Community Memorial Hosp. Toms River, N.J.

DESCRIPTION: This exhibit illustrates the efficiency of computer tomography scans of the temporomandibular joints. The clinical and radiographic features of the temporomandibular joint syndrome are presented. Cross-sectional computer tomography imaging and surgical correlation stress the morphologic variability inherent to this syndrome. Examinations of diagnostic quality were obtained with ease and no patient discomfort. A detailed illustration and discussion of the technique is presented. (Booth 213)

■

Surgical Approach to Vertebrobasilar Insufficiency.

L. N. Hopkins, M.D., Clinical Assoc. Prof. in Neurosurgery. SUNY at Buffalo.; Dept. of Neurosurgery, Dent Neurologic Institute of Millard Fillmore Hosp.-SUNY at Buffalo.

DESCRIPTION: A rational surgical approach to vertebrobasilar insufficiency is presented. Several different vascular bypass procedures are employed, depending on the anatomical location of the obstructive atherosclerotic disease. X-ray photos and diagrams are used to demonstrate the various techniques and post-operative angiograms. (Booth 214)

■

Refractive Keratoplasty—Are Glasses Obsolete?

Penny A. Asbell, M.D., Assistant Professor of Ophthalmology, Mount Sinai School of Medicine, New York City.

DESCRIPTION: New surgical techniques allow ophthalmologists to change the front surface of the eye, the cornea, so that the eye has a new refracting ability. Radial keratotomy corrects small to moderate degrees of myopia. Epikeratophakia can be used to correct aphakia, instead of intraocular lenses or glasses. These procedures can be very effective, but the long-term results are still uncertain. Surgical technique, post-op results and complications will be demonstrated and discussed. (Booth 215)

■

SYNAPS: CPAIN, A Microcomputer Program for the Differential Diagnosis of Chest Pain.

Donald P. Copley, M.D., Clinical Professor of Medicine. SUNY at Buffalo.

DESCRIPTION: SYNAPS: CPAIN is an adaptable MBasic Computer program which evaluates chest pain data. It serves as a teaching and diagnostic aid using 12 causes and 96 differential tests in a graphic format. It generates clinical simulations using Bayes Theorem. (Booth 216)

■

Successful Treatment of Morbid Obesity By Gastric Bypass.

Norman B. Ackerman, M.D., Ph.D.,—Professor of Surgery, New York Medical College, Valhalla, N.Y.

DESCRIPTION: Patients with morbid obesity generally are unable to lose weight by ordinary means. Gastric bypass has been effective in producing long term weight loss with improvement in pre-existing diabetes, hypertension, hyperlipidemia and arthritis. Postoperative complications and later metabolic problems are infrequent. Criteria for operation, operative technique and results will be displayed. (Booth 217)

■

Case histories in Exercise Testing

Venkataraman Balu, M.D., Chief, Echocardiograph Lab, VA Medical Center, Buffalo, New York

DESCRIPTION: Exercise testing is widely used in the diagnosis of coronary artery disease, assessment of drug therapy and surgery, assessment of work capacity, and cardiovascular conditioning, assessment of post-myocardial infarction patients.
This exhibit has case histories of different patients with various problems. Effort is made to highlight some of these points in individual cases. (Booth 218)

■

NYMPAC (New York Medical Political Action Committee)

Lake Success, New York

NYMPAC is the political action arm of the Medical Society of the State of New York. Its purpose: to help physicians in this state understand how government actions affect the delivery and quality of health care . . . and to help all of us take a more active and effective part in political affairs. We're a voluntary, non-profit committee of individual physicians and other interested people. We're not affiliated with any political party. We provide financial support and technical assistance in campaign planning to candidates for office whose views are consistent with our profession's concerns for sound medical care. (Booth 47)

■

Medical Society of the State of New York

Lake Success, New York

Services available to members will be depicted at the State Medical Society booth, where staff will be on hand to answer questions. Carryaway literature describes the divisions of scientific activities, scientific publications, legislation, medical services, public affairs, membership benefits, and continuing medical education.

1984 ANNUAL CME ASSEMBLY

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SHERATON CENTRE HOTEL

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AID Associates, Inc. New York City	**Booth 53**
AIS Corporation Bridgewater, New Jersey	**Booth 23**
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Advance Registration Form

Complete and return this form to the Medical Society address as indicated below.

1984 Annual CME Assembly, June 29–July 1

SHERATON CENTRE, NEW YORK CITY

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LAST *FIRST*

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- ☐ Speaker
- ☐ Medical Student
- ☐ Medical Assistant
- ☐ Resident/Intern
- ☐ Spouse/Family
- ☐ News Media

MEET THE PROFESSOR

Friday, June 29th only. Fee: $25.00 per session. Please indicate session(s) attending. The six, 1½ hour sessions are limited to 30 persons each.

- ☐ 8:30 a.m. – Stephen Scheidt, M.D.
- ☐ 10:00 a.m. – Richard Gorlin, M.D.
- ☐ 11:30 a.m. – Howard Spiro, M.D.
- ☐ 1:00 p.m. – Eli Friedman, M.D.
- ☐ 2:30 p.m. – Philip Felig, M.D.
- ☐ 4:00 p.m. – Harold Neu, M.D.

(See this issue for subjects to be presented by each Professor)

REMITTANCE

Registration Fee $ ______________
Meet the Professor session(s) $ ______________
TOTAL $ ______________

Please make check payable to:
Medical Society of the State of New York, and return this form with remittance to: Division of Meeting Services, MSSNY, 420 Lakeville Rd., P.O. Box 5404, Lake Success, N.Y. 11042.

Important: Your ID Badge will be held at the MSSNY Registration Desk located in the Exhibition Centre, lower level, Sheraton Centre.

Meet the Professor — JUNE 29th

at the Medical Society of the State of New York's Annual CME Assembly, June 29-July 1, Sheraton Centre, New York City. Three sessions, 1½ hours each, will be offered on Friday morning, and three on Friday afternoon. Sessions are limited to 30 attendees each, and there is a $25.00 fee per session. Please see the registration form on the facing page.

Philip Felig, M.D.

Professor of Medicine & Chief of Endocrinology, Yale University School of Medicine, New Haven, Connecticut. This session will deal with newer intensive approaches to the management of diabetes, including self-monitoring of blood glucose, multiple insulin injections and insulin pump therapy.

Eli A. Friedman, M.D.

Professor of Medicine, Chief, Division of Renal Disease, SUNY Downstate Medical Center, Brooklyn, N.Y. Uremia therapy is one of the great successes of this century. There are currently more than 250,000 patients sustained by maintenance hemodialysis, peritoneal dialysis, and renal transplantation. The importance of identification and appropriate preparation of candidates for these therapies is self evident. The major causes of renal failure, its conservative management, and the advantages and problems of each therapeutic option will be considered.

Richard Gorlin, M.D.

Professor & Chairman of Medicine, Mount Sinai Hospital, New York City. The causes of heart failure and certain compensatory mechanisms which are called into play to abate it, in relation to chronic heart failure.

Harold Neu, M.D.

Professor of Medicine & Pharmacology, & Chief, Division of Infectious Diseases, Columbia University College of Physicians & Surgeons, New York City. This lecture will attempt to place all of the cephalosporin antibiotics in perspective so that the practicing physician will know when to use these drugs.

Stephen Scheidt, M.D.

Professor of Clinical Medicine, New York Hospital-Cornell Medical Center, New York City. To update the practicing physician on current knowledge concerning calcium blockers, including new data on arrhythmias, vasospastic angina, chronic stable angina, IHSS, hypertension, and other current or potential indications for their use.

Howard M. Spiro, M.D.

Professor of Medicine, Yale University School of Medicine, New Haven, Connecticut. Update the practicing physician on clinical and technological advances in gastroenterology while keeping the patient's problem as a focus.

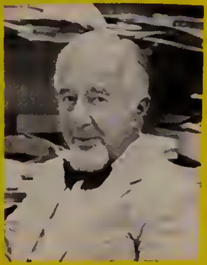
Felig

Friedman

Gorlin

Neu

Scheidt



Spiro

Gene Luttenberg

Weekend Sightseeing for the Family

During the CME Assembly, June 29–July 1

SOUTH STREET SEAPORT & LOWER NEW YORK

New York's newest place to be is just a few blocks south of the Brooklyn Bridge, on Manhattan's lower eastern waterfront. It's an 11-block historic district, where in the year 1633, this area was the center of New Amsterdam's mercantile activity. By 1800, its port had surpassed both Boston and Philadelphia's to become the busiest in America. It continued to be an active port for the tall sailing ships until the late nineteenth century when steam ships replaced the sail. Today the area is being preserved and many of the buildings and ships have undergone restoration.

PHOTOS COURTESY N Y CONVENTION & VISITORS BUREAU

THE MUSEUM BLOCK

These beautifully restored buildings reflect 200 years of construction and architectural styles. The South Street Seaport Museum office building is believed to be the oldest, constructed in 1797. The Fish Building, built in 1914, is now the Trans-Lux Seaport Theater, with a multi-screen recreation of South Street's heyday. There are 17 shops in Museum Block, including Caswell-Massey, apothecary to George Washington, Blunt's Book & Chart Store which stocks nautical books and charts, the Seaport Gallery which displays ship models, a toy store, apparel shops, and an Italian restaurant.

FULTON MARKET

The original Fulton Market, built in 1822, housed butchers, fish merchants, and produce purveyors. Today, occupying a full block, it has been rebuilt to blend with the architecture of the neighborhood. It offers three exciting floors of restaurants, cafes, and specialty food shops. On the ground floor you can buy coffee, tea, cheese, fresh vegetables and fruits, fresh fish, kitchen accessories, bread and pastry, and you may dine at the sidewalk tables of an American restaurant. On the second level are 22 separate food stalls representing every type of cuisine. On the third floor you will find an elegant restaurant with an outdoor balcony overlooking the seaport.

SCHERMERHORN ROW

Named after the shipowner and merchant, Peter Schermerhorn, this row of late Georgian-Federal commercial buildings was built in 1812. The building provided office space for counting houses, housed seamen, sail makers and other merchants. The row of 12 buildings facing the gray cobblestones of Fulton Street has been cleaned and restored. Today we find an English Pub restaurant, seafood restaurants, marine antiques, and apparel shops.

PIERS 15 AND 16

Here you may view the six moored ships. The four-masted steel bark *Peking* is one of the largest and last sailing ships built for commercial purposes. Built in 1911, she carried nitrate and fertilizer from South America to Europe. The *Wavertree,* an 1884 British full-rigged ship, built for the jute trade between India and Europe, was dismasted off Cape Horn in 1910. Also, you may view the *Ambrose* lightship built in 1907 to mark the entrance to Ambrose Channel in New York Harbor. Other vessels on view are the *Pioneer,* launched as a sloop in 1885 and later restored as a gaff-rigged schooner, plus the *Lettie G. Howard,* a Glaucester schooner built in 1893.

GRAY LINE TOURS

Doctor, we recommend that you bring your family to New York City in June where you may attend meetings at the CME Assembly and also join your family in a tour of the South Street Seaport. The Gray Line offers guided tours of lower New York and the South Street Seaport (Tour #7), and has five hourly departures daily from 9:00 a.m. to 1:00 p.m. In addition to the South Street Seaport, the tour includes views of several squares, including Washington Square, continuing to Chinatown, the Civic Center, the financial and maritime districts, Battery Park, the World Trade Center, and a ride along the East River past the U.N. to Rockefeller Center.

The tour #7 lasts about 5½ hours and departs and returns to the Gray Line terminal located at 8th Avenue and 54th Street, just two blocks from the Sheraton Centre Hotel. The tour price is $19.50, and tickets may be purchased at the theatre/tour desk in the lobby of the Sheraton Centre Hotel.

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New York State Journal of Medicine

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MEETINGS AND LECTURES

MAY 1984

AROUND THE STATE

MANHATTAN

May 3. **Cancer Chemotherapy.** 1.5 Cat 1 credits. *May 5.* **Breast Cancer.** 3.5 Cat 1 credits. Info: Clifford L Spingarn, MD, Chairman, Committee on Continuing Medical Education, Doctors Hospital, 170 East End Ave, New York, NY 10028. Tel: (212) 870-9000.

May 3-5. **The Medicolegal Autopsy.** 15 Cat 1 credits. *May 10-13.* **CT of the Spine.** 16 Cat 1 credits. *May 19-20.* **Review of Basic Sciences in Urology.** 14 Cat 1 credits. *May 19-20.* **Proficiency in Cytopathology.** 13 Cat 1 credits. *May 17-20.* **Practical Management of Gynecologic Endocrine Disorders and Infertility.** 16 Cat 1 credits. Info: Elaine Breslow, NYU Post-Graduate Medical School, 550 First Ave, New York, NY 10016. Tel: (212) 340-5295.

May 4. **Management of Stroke: Medical, Neurological and Rehabilitation Aspects.** 5.5 Cat 1 credits. *May 18.* **Muscle Disease Update.** 4 Cat 1 credits. *May 23.* **Hypertension.** 6.5 Cat 1 credits. *May 25.* **Pediatric Rehabilitation in the Child with Chronic Pulmonary Disease.** 4.5 Cat 1 credits. Info: Beverley R Baptiste, Continuing Medical Education, Beth Israel Hospital, 10 Nathan D Perlman Place, New York, NY 10003. Tel: (212) 420-2000.

May 6-10. **Advances in Pulmonary Medicine.** Info: Maxine Topping, Postgraduate Education Dept, American College of Physicians, 4200 Pine Street, Philadelphia, PA 19104. Tel: (215) 243-1200 or (800) 523-1546.

May 12. **Clinical Pathology.** 2 Cat 1 credits. Info: Victor Tchertkoff, MD, Director of Laboratories, Metropolitan Hospital Center, 1901 First Ave, New York, NY 10029. Tel: (212) 360-6253.

(*Continued on page 42A*)

AMERICAN ASSOCIATION OF COSMETIC SURGEONS ANNOUNCES THE

INTERNATIONAL CONGRESS FOR HAIR REPLACEMENT SURGERY

JUNE 14–16, 1984
Plaza Hotel, New York City

The Hair Replacement Congress is an advanced seminar in hair replacement surgery with an innovative format on new and improved procedures by internationally known hair replacement surgeons. The program will feature multidiscipline speaker participants with keynote addresses, and panel and participant discussions. Free papers of 5 to 15 minutes in length are requested for selection. Send abstracts to: D.B. Stough, III, M.D., Congress Director. Address below.

HONORING NORMAN ORENTREICH, M.D., 25th ANNIVERSARY FOR HAIR TRANSPLANTATION

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For additional information, please contact: D.B. Stough, III, M.D., Congress Director, The Stough Dermatology & Cutaneous Surgery Clinic, P.A., Doctors Park, Hot Springs, AR 71901. (501) 624-0673.

■

ANNUAL SCIENTIFIC MEETING OF THE AMERICAN ASSOCIATION OF COSMETIC SURGEONS

JUNE 16–17, 1984
Plaza Hotel, New York City

The American Association of Cosmetic Surgeons annual scientific meeting will be held following the International Congress for Hair Replacement Surgery. Robert Wood, M.D., P.S., Houston, Texas will be program director. The annual meeting will discuss the most advanced techniques and trends in the following topics: Anesthetic Body Sculpting-Liposuction; Rhinoplasty; Facial Rejuvenation; Aesthetic Office Procedures; Aesthetic Procedures of the Eyelid.

For more information contact: Pierre Guibor, M.D., President, American Association of Cosmetic Surgeons, 630 Park Ave., New York, N.Y. 10021.

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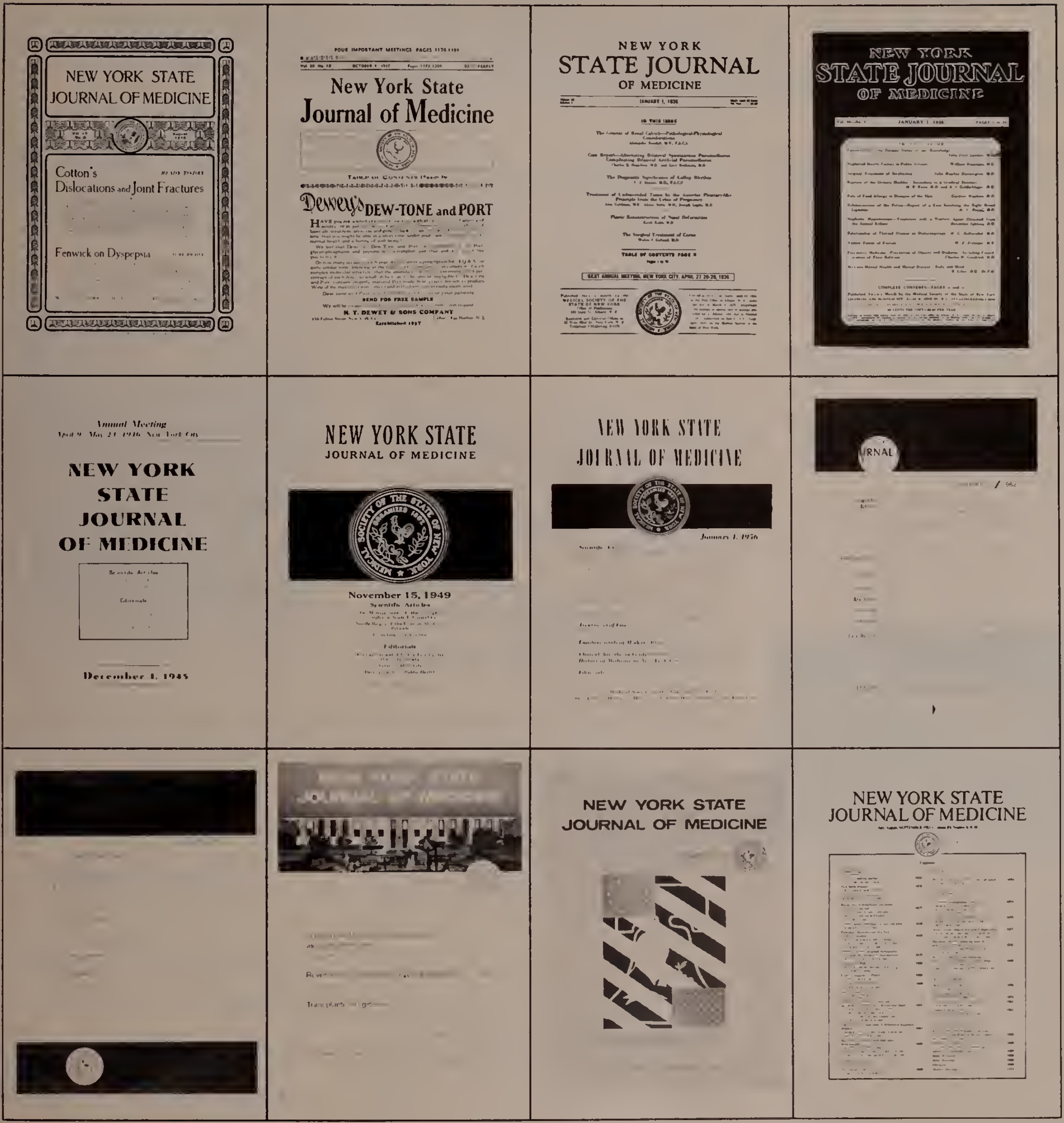
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JANUARY 1, 1936

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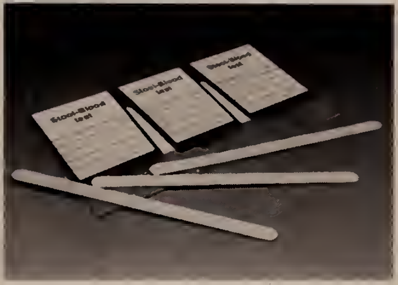

The presence of hidden blood usually indicates some problem in the stomach or bowel, not necessarily cancer. Positive tests must be followed by further testing to find out what the problem is.

Other tests for colorectal cancer you should talk to your doctor about: digital rectal exam (after age 40); the procto test (after age 50). It is important to report any personal or family history of intestinal polyps or ulcerative colitis, and any change in your bowel habits, which could be a cancer warning signal.

The American Cancer Society wants you to know.

AMERICAN CANCER SOCIETY®

(*Continued from page 39A*)

May 14–18. **Temporal Bone Surgery.** 40 Cat 1 credits. Info: The Page and William Black Postgraduate School of Medicine of the Mount Sinai School of Medicine, One Gustave Levy Pl, New York, NY 10029. Tel: (212) 650-6546.

May 16. **Update Your Medicine.** Info: Lila A Wallis, MD, Chairman, Continuing Medical Education Program, The Association of Practicing Physicians of the New York Hospital, 1300 York Ave, Room D-115, New York, NY 10021. Tel: (212) 737-4444, or Dena Toussaint (212) 472-6119.

May 17–18. **Sports Medicine Today.** 16 Cat 1 credits. *May 30.* **A Clinical Day in Ophthalmology: Ocular Inflammation.** 7 Cat 1 credits. Info: Ann J Boehme, Continuing Education Coordinator, Long Island Jewish-Hillside Medical Center, New Hyde Park, NY. Tel: (212) 470-2114.

May 17–19. **Electrodiagnosis of Peripheral Neurological Lesions.** 16 Cat 1 credits. Info: John Flynn, MD, Dept of Medicine, NY Infirmary-Beekman Downtown Hospital, New York, NY 10038. Tel (212) 233-5300.

May 23. **Contemporary Health Care for the Elderly in 1984: The Multidisciplinary Team Approach to Problems of the Aging Patient.** 5 Cat 1 credits. Info: Louis Sod, MD, Coler Memorial Hospital, NY Medical College, Roosevelt Island, NY 10044. Tel: (212) 688-9400 Ext. 550.

May 31–June 3. **New York Ophthalmic Surgery Congress.** Info: K Zinn, MD, NY Ophthalmic Surgery Headquarters, 630 Park Ave, New York, NY 10021. Tel: (212) 734-1010 or (800) 223-4500.

BROOKLYN

May 20. **Infections of the Upper and Lower Respiratory Tracts.** Info: Claudia Troiano, Registrar and Coordinator, Pediatric Dept, Maimonides Medical Center, 4802 10th Ave, Brooklyn, NY 11219. Tel: (212) 270-7679.

QUEENS

May 1. **Treatment of Hypertension.** *May 8.* **Sudden Cardiac Death: An Overview.** *May 15.* **Patients' Rights & the Death of the Hippocratic Ethic.** *May 22.* **Symposium on Geriatric Medicine.** *May 29.* **Cost-Containment: A Critical Appraisal.** Info: Clo Vezza, Coordinator, CME Committee, Booth Memorial Medical Center, 56-45 Main St, Flushing, NY 11355. Tel: (212) 670-1231.

May 16. **Adolescence, A Problem Time of Life.** 5 Cat 1 credits. Info: Evelyn R Barkin, Dept of Pediatrics, Jamaica Hospital, 89th Ave and Van Wyck Expressway, Jamaica, NY 11418. Tel: (212) 557-1800, ext 1751.

NASSAU

May 4. **Cellular Effects of Perinatal Asphyxia.** *May 11.* **Clinical Pathology Conference.** *May 18.* **Drug Withdrawal Syndrome in the Newborn.** Info: Clement Boccalini, MD, Assist Dean, Undergraduate and CME, Nassau County Medical Center, 2201 Hempstead Turnpike, East Meadow, NY 11554. Tel: (516) 542-0123.

ERIE

May 12. Molecular Biology and Its Relevance to the Treatment of Colon Cancer. Info: Gayle Bersani, RN, Cancer Control

(*Continued on page 43A*)

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(*Continued from page 42A*)

Coordinator, Roswell Park Memorial Institute, 666 Elm St, Buffalo, NY 14263. Tel: (716) 845-4406.

OSTEGO

May 10. **Managing Illness in the Elderly.** 3 Cat 1 credits. Oneonta. Info: Bonnie Kaido, Medical Education Coordinator, The Mary Imogene Bassett Hospital, Cooperstown, NY 13326. Tel: (607) 547-3764.

SULLIVAN

May 18-20. **NY State Academy of Family Physicians (Congress of Delegates).** *May 21-23.* **NY State Academy of Family Physicians (Scientific Assembly).** Monticello. Info: Donna E Lewis, Exec Sec, NY State Acad of Family Physicians, 30 West State St, Colonial Plaza, Binghamton, NY 13901. Tel: (607) 722-7205.

AROUND THE NATION

ARIZONA

May 10-11. **Successful Hospital Management Under DRG Based Prospective Pricing.** Phoenix. Info: Registrar, Commission of Professional and Hospital Activities, 1968 Green Rd, PO Box 1809, Ann Arbor, MI 48106. Tel: (800) 521-6210, ext 348.

CALIFORNIA

May 3-6. **Psychoanalysis, Communication Technologies and the Media.** Los Angeles. Vivian Mendelsohn, Admin Dir, The American Academy of Psychoanalysis, 30 East 40 St, New York, NY 10016. Tel: (212) 679-4105.

COLORADO

May 15-18. **American Geriatrics Society, Scientific Meeting.** Denver. Info: Linda Hiddemen Barondess, Exec Vice Pres, American Geriatrics Society, 10 Columbus Circle, New York, NY 10019. Tel: (212) 582-1333.

ILLINOIS

May 11-13. **Psychosocial Aspects of the Family: The New Pediatrics.** 17 Cat 1 credits. Chicago. Info: Steven Sawchuk, MD, Institute for Pediatric Service, Johnson & Johnson Baby Products Company, Grandview Road, Skillman, NJ 08558. Tel: (201) 874-1646/1645.

May 11-14. **Review and Update of Emergency Medicine: Cardiovascular/Pulmonary.** 35 Cat 1 credits. Chicago. Info: Registrar, American College of Emergency Physicians, PO Box 61991, Dallas, TX 75261-9911. Tel: (214) 659-0911.

May 29-June 9. **Specialty Review in Family Practice.** 91 Cat 1 credits. *May 14-19.* Specialty Review in Obstetrics and Gynecology. 48 Cat 1 credits. Chicago. Info: M LeRoy Sprang, MD, The Cook County Graduate School of Medicine, 707 South Wood St, Chicago, IL 60612. Tel: (312) 733-2800.

KENTUCKY

May 20-25. **Family Medicine Review.** 50 Cat 1 credits. Lexington. Info: Joy Greene, University of Kentucky College

(*Continued on page 44A*)

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1-800-822-8838

(*Continued from page 43A*)

of Medicine, CME, University of Kentucky, Lexington, KY 40536-0086. Tel: (606) 233-5161.

LOUISIANA

May 7–11. **Workshop on the Management of Leprosy Training.** New Orleans. Info: W Felton Ross, American Leprosy Missions, One Broadway, Elmwood Park, NJ 07407. Tel: (201) 794-8650.

MASSACHUSETTS

May 7–18. **Emergency Care: An Extended Workshop.** 80 Cat 1 credits. Boston. Info: Barbara Wagner, Medical Education Unit, Massachusetts General Hospital, Boston, MA 02114. Tel: (617) 726-3905.

May 10–12. **Topics in Internal Medicine.** 15 Cat 1 credits. Boston. Info: Department of Education, LCF Foundation, Inc, 41 Mall Rd, Burlington, MA 01803. Tel: (617) 273-5100.

May 25–27. **Symposium on Problems in Suction Lipectomy.** 16 Cat 1 credits. Boston. Info: Registrar Plastic Surgery Education Foundation, 233 N Michigan Ave, Suite 1900, Chicago, IL 60601. Tel: (312) 856-1818.

MISSOURI

May 12–13. **Reading a Chest X-Ray: An Integrated Anatomical, Physiological, Pathological Approach.** 20 Cat 1 credits. St Louis. Info: Mary J Ryals, Ryals and Associates, PO Box 61203, DFW Airport, TX 75261. Tel: (214) 659-9590.

NEBRASKA

May 7–18. **Family Practice Review: Comprehensive Update.** 100 Cat 1 credits. Omaha. Info: Marge Adey, Center for Continuing Education, University of Nebraska College of Medicine, 42nd and Dewey, Omaha, NE 68105. Tel: (402) 559-4152.

NEVADA

May 31–June 2. **Reorganization: The Next Decade—Corporate Systems & New Ventures Strategy.** Las Vegas. Info: Registrar, Aspen Systems Corp, 1600 Research Blvd, Rockville, MD 20850. Tel: (301) 251-5290.

NEW JERSEY

May 14–15. **Vascular Symposium.** 14.5 Cat 1 credits. Atlantic City. Info: Patricia C Sarles, UMDNJ-New Jersey Medical School, 100 Bergen St, Newark, NJ 07103. Tel: (201) 456-4267.

OHIO

May 11–12. **Clinical Approach to Arterial Blood Gas Interpretation & Electrolytes.** 13.5 Cat 1 credits. Akron. Info: Postgraduate Division, American College of Physicians, 4200 Pine St, Philadelphia, PA 19104. Tel: (215) 243-1546.

OKLAHOMA

May 31–June 2. **Cytopathology and Public Health: Applications and Clinical Management.** 17 Cat 1 credits. Oklahoma City. Info: Magdalen De Bault, University of Oklahoma College of Medicine, Office of CME, PO Box 26307, Room 5N301, Oklahoma City, OK 73126. Tel: (405) 271-5663.

(*Continued on page 46A*)

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Listen, this is important. You see your insides down there? Sure, your heart and your brain and all that stuff is there. But look at your lungs! I mean they are important! Without your lungs, nothing works! So don't smoke. Because smoking, oh, it's terrible! Your lungs get darker and get damaged. Smoking makes your lungs work harder and harder until, whew! You can't breathe at all! So don't smoke. That's all.

Sid Caesar

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(Continued from page 44A)

PENNSYLVANIA

May 3–5. **Common Clinical Challenges in the Elderly.** 16.25 Cat 1 credits. Philadelphia. Info: Nancy Spaw, Dept of Medicine, Philadelphia Geriatric Center, 5301 Old York Road, Philadelphia, PA 19141. Tel: (215) 456-2900.

SOUTH CAROLINA

May 18–20. **Providing Quality Medical Care in Your Practice.** Hilton Head. Info: Jeanette Stone, Southern Medical Association, PO Box 2446, Birmingham, AL 35201. Tel: (205) 323-4400.

TENNESSEE

May 30–June 2. **Spring Seminar in Anesthesiology.** Hilton Head Island. Info: Program Director, American Academy of Clinical Anesthesiologists, PO Box 11691, Knoxville, TN 37939-1681. Tel: (615) 588-6279.

WEST VIRGINIA

May 9–12. **Spring Ophthalmology Meeting.** 16 Cat 1 credits. White Sulfur Springs. Info: James R Cook, MD, Secretary-Treasurer, West Virginia Academy of Ophthalmology, 1616 13th Ave, Huntington, WV 25701. Tel: (304) 529-7366.

AROUND THE WORLD

CANADA

May 9–12. **American Association for Cancer Research, Annual Meeting.** Hour-for-hour Cat 1 credits. Toronto. Info: Margaret Foti, Exec Dir, AACR, Temple University School of Medicine, West Building, Room 301, Philadelphia, PA 19140. Tel: (215) 221-4565.

CHINA

May 4–May 20; May 11–May 27. **Physician to Physician.** 30 Cat 1 credits. Info: First National Professional Congresses, Inc. PO Box 268, Passaic, NJ 07055. Tel: (516) 766-3000, (212) 454-9595, (800) 221-7179.

ENGLAND

May 5–13. **Endocrinology in Primary Care Clinical Practice.** London. Info: Cynthia Vaughan, Health Science Seminars, PO Box 22023, San Francisco, CA 94122. Tel: (415) 861-2713.

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EMERGENCY MEDICINE—full time position. Established ER group, upstate NY. Teaching opportunity available. Salary competitive. New York license required. Send CV to: Kevin Ohara, Physician Service Associates, 305 Main Street, Johnson City, NY 13790. (607) 729-0859 or 798-0076.

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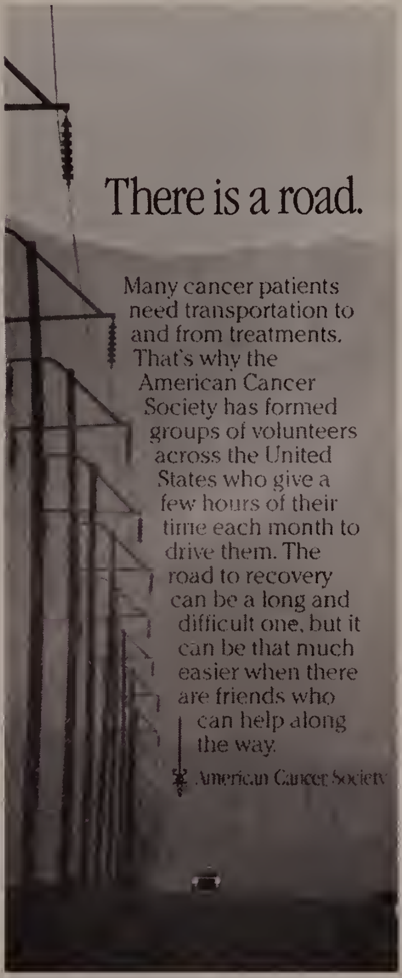

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Many cancer patients need transportation to and from treatments. That's why the American Cancer Society has formed groups of volunteers across the United States who give a few hours of their time each month to drive them. The road to recovery can be a long and difficult one, but it can be that much easier when there are friends who can help along the way.

American Cancer Society

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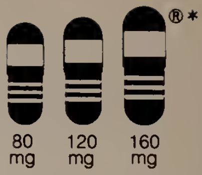

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INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period

The mechanism of the antihypertensive effect of INDERAL has not been established Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain.

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope INDERAL LA also improves exercise performance The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL

WARNINGS. CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

> IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers

DIABETES AND HYPOGLYCEMIA: Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker In one case this resulted after an initial dose of 5 mg propranolol

PRECAUTIONS. *General:* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure Patients should be told that INDERAL may interfere with the glaucoma screening test Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity There were no drug-related tumorigenic effects at any of the dosage levels Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug

Pregnancy: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose There are no adequate and well-controlled studies in pregnant women INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Nursing Mothers. INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia, congestive heart failure; intensification of AV block, hypotension; paresthesia of hands; thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System. lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia, visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress

Respiratory: bronchospasm

Hematologic. agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval

HYPERTENSION—*Dosage must be individualized* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved The usual maintenance dosage is 120 to 160 mg once daily In some instances a dosage of 640 mg may be required The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS)

MIGRAINE—*Dosage must be individualized* The initial oral dose is 80 mg INDERAL LA once daily The usual effective dose range is 160-240 mg once daily The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued It may be advisable to withdraw the drug gradually over a period of several weeks

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use

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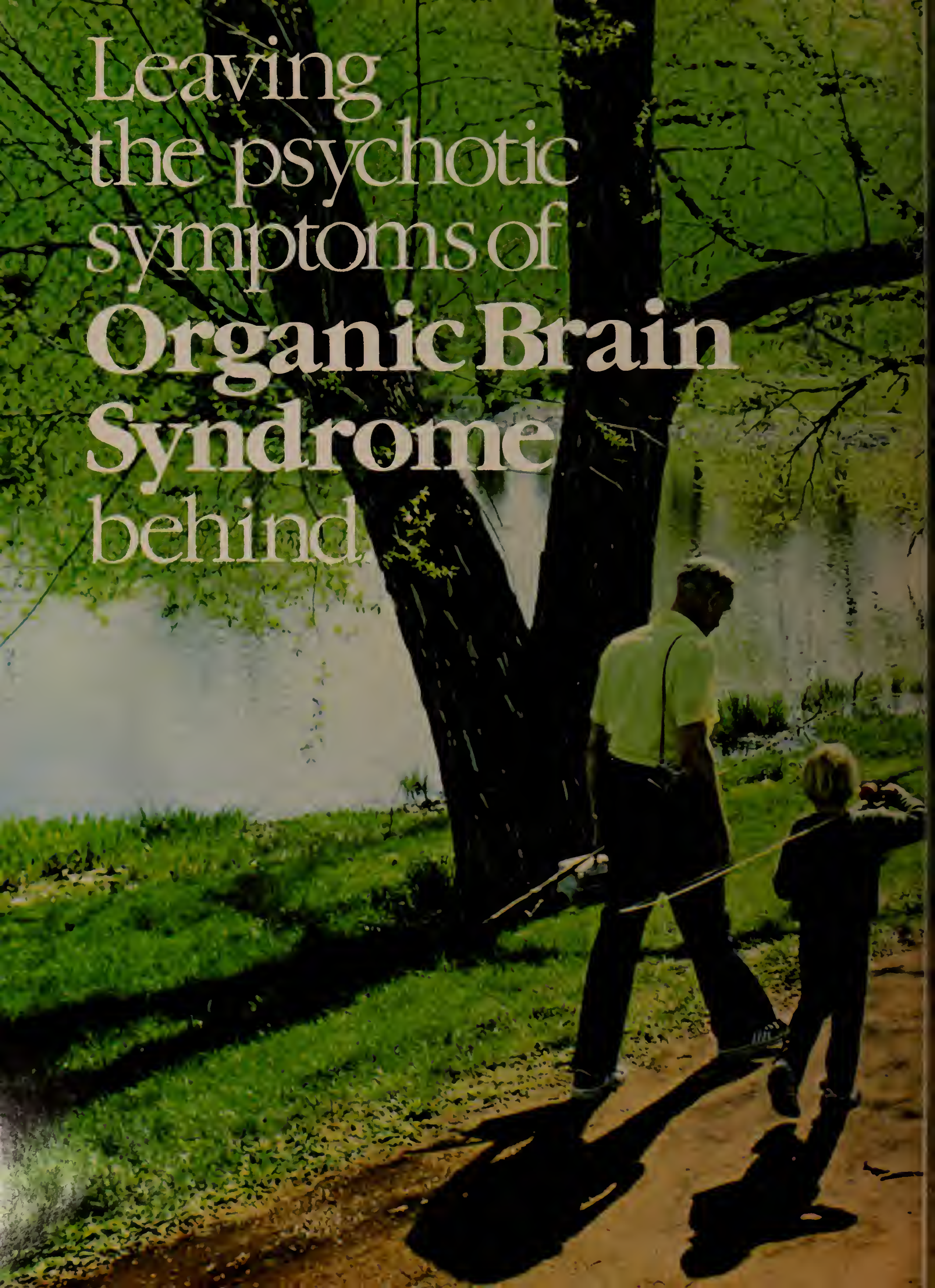
Leaving the psychotic symptoms of
Organic Brain Syndrome
behind.

Effective

Treatment with Navane can produce improvement in psychotic symptoms such as hallucinatory behavior and unusual thought content as well as hostility, disorientation and depressive mood,[1,2] leaving the elderly patient more alert[2] and better able to participate in the activities of family life.

Well tolerated

Navane is generally well tolerated by elderly patients. Excessive sedation or drowsiness has been reported, but is uncommon.[1] Anticholinergic effects[3] and hypotension[4,5] are reported, but rarely. Should they occur, extrapyramidal symptoms can usually be readily controlled.

Navane®

(thiothixene) (thiothixene HCl)

Capsules 1 mg, 2 mg, 5 mg, 10 mg, 20 mg
Concentrate 5 mg/ml Intramuscular 2 mg/ml, 5 mg/ml

See following page for a brief summary of prescribing information.

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Navane®

(thiothixene) (thiothixene HCl)

References. 1 Util TM, Unverdı C. Wohlrade J, et al: Drug therapy of psychosis associated with organic brain syndrome Presented as a Scientific Exhibit at the American Public Health Association Centennial, Atlantic City. New Jersey, November 12-16, 1972. 2. Katz MM, Util TM. Video methodology for research in psychopathology and psychopharmacology. *Arch Gen Psychiatry* 31:204-210, 1974. 3. Ketai R Psychotropic drugs in the management of psychiatric emergencies. *Postgraduate Medicine* 58 87-93, 1975. 4 Birkett DP, Hirschfield W, Simpson GM Thiothixene in the treatment of diseases of the senium *Curr Ther Res* 14 775-779, 1972. 5. Data on file at Roerig.

BRIEF SUMMARY OF PRESCRIBING INFORMATION
Navane® (thiothixene) Capsules: 1 mg, 2 mg, 5 mg, 10 mg, 20 mg
(thiothixene hydrochloride) Concentrate: 5 mg/ml, Intramuscular: 2 mg/ml, 5 mg/ml

Contraindications: Navane (thiothixene) is contraindicated in patients with circulatory collapse, comatose states, central nervous system depression due to any cause, and blood dyscrasias Navane is contraindicated in individuals who have shown hypersensitivity to the drug It is not known whether there is a cross-sensitivity between the thioxanthenes and the phenothiazine derivatives, but the possibility should be considered

Warnings: *Usage in Pregnancy* – Safe use of Navane during pregnancy has not been established Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus Animal reproduction studies and clinical experience to date have not demonstrated any teratogenic effects.

In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen. (See Precautions)

Usage in Children – The use of Navane in children under 12 years of age is not recommended because safety and efficacy in the pediatric age group have not been established.

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy Therefore, the patient should be cautioned accordingly

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol

Precautions: An antiemetic effect was observed in animal studies with Navane, since this effect may also occur in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumor.

In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold. Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered concurrently

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with other CNS depressants other than anticonvulsant drugs

Though exhibiting rather weak anticholinergic properties, Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving atropine or related drugs

Use with caution in patients with cardiovascular disease

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine lenticular pigmentation has been noted in a small number of patients treated with Navane for prolonged periods) Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenic purpura), and liver damage (jaundice, biliary stasis) have been reported with related drugs.

Undue exposure to sunlight should be avoided Photosensitive reactions have been reported in patients on Navane.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis, the available evidence is considered too limited to be conclusive at this time.

Intramuscular Administration – As with all intramuscular preparations, Navane Intramuscular should be injected well within the body of a relatively large muscle The preferred sites are the upper outer quadrant of the buttock (i.e gluteus maximus) and the mid-lateral thigh

The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury Intramuscular injections should not be made into the lower and mid-thirds of the upper arm As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel

Adverse Reactions: *Note* Not all of the following adverse reactions have been reported with Navane (thiothixene). However, since Navane has certain chemical and pharmacologic similarities to the phenothiazines, all of the known side effects and toxicity associated with phenothiazine therapy should be borne in mind when Navane is used

Cardiovascular effects Tachycardia, hypotension, lightheadedness, and syncope In the event hypotension occurs, epinephrine should not be used as a pressor agent since a paradoxical further lowering of blood pressure may result Nonspecific EKG changes have been observed in some patients receiving Navane These changes are usually reversible and frequently disappear on continued Navane therapy The incidence of these changes is lower than that observed with some phenothiazines The clinical significance of these changes is not known

CNS effects: Drowsiness, usually mild, may occur although it usually subsides wtih continuation of Navane therapy The incidence of sedation appears similar to that of the piperazine group of phenothiazines, but less than that of certain aliphatic phenothiazines Restlessness, agitation and insomnia have been noted with Navane (thiothixene) Seizures and paradoxical exacerbation of psychotic symptoms have occurred with Navane infrequently

Hyperreflexia has been reported in infants delivered from mothers having received structurally related drugs

In addition phenothiazine derivatives have been associated with cerebral edema and cerebrospinal fluid abnormalities

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia and dystonia have been reported Management of these extrapyramidal symptoms depends upon the type and severity Rapid relief of acute symptoms may require the use of an injectable antiparkinson agent More slowly emerging symptoms may be managed by reducing the dosage of Navane and/or administering an oral antiparkinson agent

Persistent Tardive Dyskinesia As with all antipsychotic agents tardive dyskinesia may appear in some patients on long term therapy or may occur after drug therapy has been discontinued. The risk seems to be greater in elderly patients on high-dose therapy, especially females The symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g , protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities

There is no known effective treatment for tardive dyskinesia, antiparkinsonism agents usually do not alleviate the symptoms of this syndrome It is suggested that all antipsychotic agents be discontinued if these symptoms appear

Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, the syndrome may be masked

It has been reported that fine vermicular movements of the tongue may be an early sign of the syndrome and if the medication is stopped at that time, the syndrome may not develop.

Hepatic effects: Elevations of serum transaminase and alkaline phosphatase, usually transient, have been infrequently observed in some patients. No clinically confirmed cases of jaundice attributable to Navane (thiothixene) have been reported.

Hematologic effects: As is true with certain other psychotropic drugs, leukopenia and leukocytosis, which are usually transient, can occur occasionally with Navane Other antipsychotic drugs have been associated with agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopenia

Allergic reactions Rash, pruritus, urticaria, photosensitivity and rare cases of anaphylaxis have been reported with Navane Undue exposure to sunlight should be avoided Although not experienced with Navane, exfoliative dermatitis and contact dermatitis (in nursing personnel) have been reported with certain phenothiazines

Endocrine disorders. Lactation, moderate breast enlargement and amenorrhea have occurred in a small percentage of females receiving Navane If persistent, this may necessitate a reduction in dosage or the discontinuation of therapy Phenothiazines have been associated with false positive pregnancy tests, gynecomastia, hypoglycemia, hyperglycemia, and glycosuria

Autonomic effects Dry mouth, blurred vision, nasal congestion, constipation, increased sweating, increased salivation, and impotence have occurred infrequently with Navane therapy Phenothiazines have been associated with miosis, mydriasis, and adynamic ileus.

Other adverse reactions. Hyperpyrexia, anorexia, nausea, vomiting, diarrhea, increase in appetite and weight, weakness or fatigue, polydipsia and peripheral edema

Although not reported with Navane, evidence indicates there is a relationship between phenothiazine therapy and the occurrence of a systemic lupus erythematosus-like syndrome

NOTE. Sudden deaths have occasionally been reported in patients who have received certain phenothiazine derivatives In some cases the cause of death was apparently cardiac arrest or asphyxia due to failure of the cough reflex In others, the cause could not be determined nor could it be established that death was due to phenothiazine administration.

Dosage and Administration: Dosage of Navane should be individually adjusted depending on the chronicity and severity of the condition. In general, small doses should be used initially and gradually increased to the optimal effective level, based on patient response.

Some patients have been successfully maintained on once-a-day Navane therapy

Usage in children under 12 years of age is not recommended because safe conditions for its use have not been established

Navane Intramuscular Solution: Navane For Injection – Where more rapid control and treatment of acute behavior is desirable, the intramuscular form of Navane may be indicated It is also of benefit where the very nature of the patient's symptomatology, whether acute or chronic, renders oral administration impractical or even impossible

For treatment of acute symptomatology or in patients unable or unwilling to take oral medication, the usual dose is 4 mg of Navane Intramuscular administered 2 to 4 times daily Dosage may be increased or decreased depending on response Most patients are controlled on a total daily dosage of 16 to 20 mg The maximum recommended dosage is 30 mg/day An oral form should supplant the injectable form as soon as possible It may be necessary to adjust the dosage when changing from the intramuscular to oral dosage forms. Dosage recommendations for Navane (thiothixene) Capsules and Concentrate appear in the following paragraphs

Navane Capsules: Navane Concentrate – In milder conditions, an initial dose of 2 mg three times daily If indicated, a subsequent increase to 15 mg/day total daily dose is often effective

In more severe conditions, an initial dose of 5 mg twice daily

The usual optimal dose is 20 to 30 mg daily If indicated, an increase to 60 mg/day total daily dose is often effective Exceeding a total daily dose of 60 mg rarely increases the beneficial response

Overdosage: Manifestations include muscular twitching, drowsiness, and dizziness Symptoms of gross overdosage may include CNS depression, rigidity, weakness, torticollis, tremor, salivation, dysphagia, hypotension, disturbances of gait, or coma

Treatment. Essentially is symptomatic and supportive. For Navane oral, early gastric lavage is helpful. For Navane oral and Intramuscular, keep patient under careful observation and maintain an open airway, since involvement of the extrapyramidal system may produce dysphagia and respiratory difficulty in severe overdosage If hypotension occurs, the standard measures for managing circulatory shock should be used (I V fluids and/or vasoconstrictors)

If a vasoconstrictor is needed, levarterenol and phenylephrine are the most suitable drugs Other pressor agents, including epinephrine, are not recommended, since phenothiazine derivatives may reverse the usual pressor action of these agents and cause further lowering of the blood pressure

If CNS depression is present and specific therapy is indicated recommended stimulants include amphetamine, dextroamphetamine, or caffeine and sodium benzoate Stimulants that may cause convulsions (e.g picrotoxin or pentylenetetrazol) should be avoided Extrapyramidal symptoms may be treated with antiparkinson drugs

There are no data on the use of peritoneal or hemodialysis, but they are known to be of little value in phenothiazine intoxication

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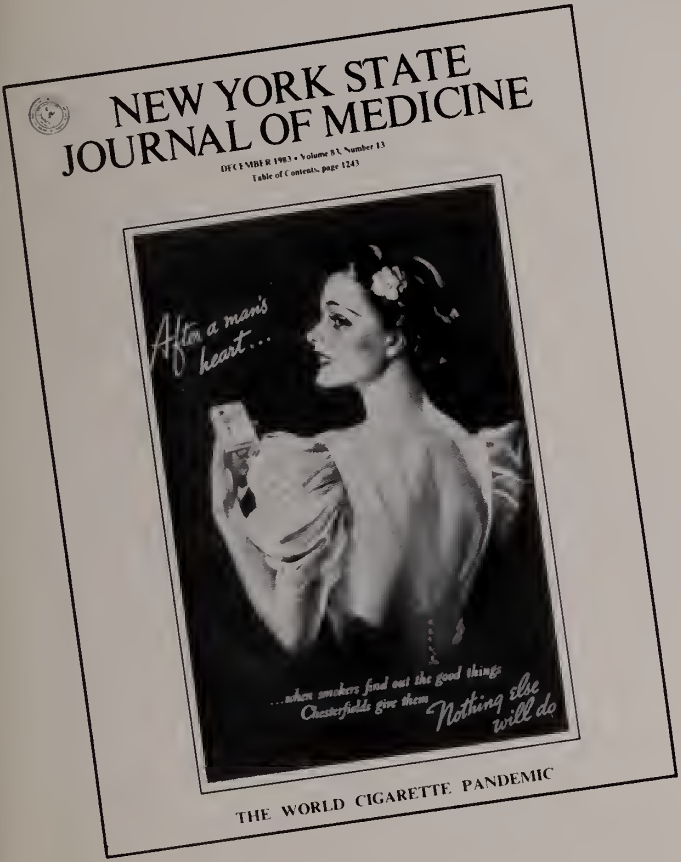

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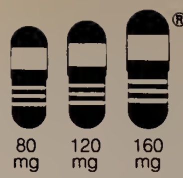

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In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity.

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain.

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

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Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS. CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

> IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. *General:* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block, hypotension; paresthesia of hands; thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia, visual disturbances, hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized.* The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily.

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

*The appearance of INDERAL LA capsules is a registered trademark of Ayerst Laboratories.

8833/384

Ayerst.

AYERST LABORATORIES
New York, N.Y. 10017

1984 ANNUAL CME ASSEMBLY

Medicine in this Age of Violence

PRESENTED BY THE

Medical Society of the State of New York

JUNE 29 - JULY 1

Sheraton Centre
Seventh Ave. & 52nd St.

New York City

□

HIGHLIGHTS . . .

General Session: Medicine in this Age of Violence • 26 Sessions • Panel Discussions • Meet the Professor • Scientific & Technical Exhibits • Medical Society Reception

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Arrival date ______ Hour ______ No. of persons ______ Departure date ______

Circle preferred rates

Single Room	$76	$84	$98
Double/Twin	$88	$98	$114
Suite	$300 and Up		

Medical Society
of the
State of New York
June 29–July 1, 1984

Reservations must be received by hotel no later than June 8.
IF RATE REQUESTED IS NOT AVAILABLE, NEXT AVAILABLE RATE WILL APPLY, RESERVATIONS RECEIVED AFTER SPECIFIED DATE WILL BE ACCOMMODATED ON A RATE AND SPACE AVAILABILITY BASIS ONLY.

Checkout time is 1:00 p.m. Normal Check in time is after 3:00 p.m.

Reservations are held until 6:00 p.m. unless guaranteed by a one nights deposit or guaranteed with one of the following credit cards: Diners Club, Carte Blanche, American Express.

Credit Card # ______ Exp. date ______ Type ______

General Information

Our CME Sessions are open to all physicians and the allied professions. The three full days of meetings will provide the individual physician with a possible 25 credits out of a total of 100, Category 1, CME credit hours being offered. Over 120 outstanding speakers, including a number from out-of-state, will present papers at 26 sessions. A highlight of the Assembly will be a general session on "Medicine in this Age of Violence," to be presented on Saturday, June 30th. Some areas to be discussed will be violence on the highway, in sports, in institutions, in war, sexual abuse of children, and drug abuse in adolescents.

Returning by popular request, "Meet the Professor" sessions will take place on Friday, June 29th. There will be six, 1½ hour sessions scheduled throughout the day.

Our program covers a wide range of medical specialties and focuses on helping the practicing physician meet the daily needs of patient care. You can be assured of an interesting program.

In addition, there will be Scientific and Technical Exhibits on display to update the physician on developments in both areas. Complimentary coffee breaks will be scheduled in the mornings and afternoons to allow time for physicians to visit the exhibits.

A reception for physicians and exhibitors, compliments of the Medical Society of the State of New York, will be held on Friday, June 29, from 6-7 pm. As the Assembly date closely precedes the 4th of July, we suggest that you bring your family to enjoy a pre-holiday weekend in New York City before continuing to your destination. The Sheraton Centre provides valet parking for your convenience.

Among the many new attractions in New York City are the downtown *South Street Seaport Museum,* a restoration of the early 19th century seaport that was engaged in trade and commerce. Here we find historic sailing ships at Pier 16, a multi-screen movie presentation of the early trading days, the Fulton Market with its restaurants, cafes, food shops, plus many specialty shops in the area. Uptown on Fifth Ave., the new *Trump Tower* presents a breathtaking, multilevel atrium lobby lined in pink marble, waterfalls and tropical plants. Escalators take you to international shops on each level. Visit the legendary WWII Aircraft Carrier *Intrepid, Sea-Air Space Museum* at Pier 86, a must experience for the entire family. Bring your family and join your colleagues for a weekend of stimulating CME sessions.

HOTEL RESERVATIONS

Physicians must make their own hotel reservation no later than June 8, 1984. If making reservations by telephone, please identify the Medical Society meeting for the special rate to apply.

REGISTRATION

Registration will take place in the Exhibition Centre, located on the lower level of the hotel. For those who registered in advance, your ID Badge will be held at the Medical Society Registration Desk. All new registrants must present identification at the registration desk.

REGISTRATION HOURS

Friday & Saturday —
8:30 a.m.-5:00 p.m.
Sunday — 8:30 a.m.-4:30 p.m.

MEETING HOURS

Friday — Meet the Professor,
8:30 a.m.-5:30 p.m.
All other meetings,
9:00 a.m.-5:00 p.m.
Saturday & Sunday —
9:00 a.m.-5:00 p.m.

1984 ANNUAL CME ASSEMBLY

Medical Society of the State of New York
Sheraton Centre, New York City

FRIDAY, JUNE 29

Morning
Cardiovascular Diseases, Royal Ballroom A
Cancer Update, Versailles Terrace
Pediatrics/School Health, Royal Ballroom B (all day)
Meet the Professor, Consulate Suite
Regency Foyer

Afternoon
Pediatrics/School Health, Royal Ballroom B
Neurosurgery, Versailles Terrace
Medical Legal & Workers' Compensation/Occupational Medicine, Royal Ballroom A
Neurology, Regency Ballroom
Meet the Professor, Consulate Suite
Regency Foyer

SATURDAY, JUNE 30

Morning
Chest Diseases, Regency Ballroom
Internal Medicine, Georgian Ballroom A (all day)
Ophthalmology, Royal Ballroom A (all day)
General Session "Violence", Georgian Ballroom B (all day)
Obstetrics/Gynecology, Versailles Terrace
Hand Surgery, Royal Ballroom B (all day)

Afternoon
Internal Medicine, Georgian Ballroom A
Ophthalmology, Royal Ballroom A
General Session "Violence", Georgian Ballroom B
Dermatology/Otolaryngology, Versailles Terrace
Pathology/Gastroenterology, Regency Ballroom
Hand Surgery, Royal Ballroom B

SUNDAY, JULY 1

Morning
Allergy & Immunology, Georgian Ballroom A
Family Practice/Preventive Medicine/Psychiatry, Versailles Terrace (all day)
Orthopedic Surgery/General Surgery/Plastic Surgery/Physical Medicine & Rehabilitation/Radiology/Anesthesiology, Georgian Ballroom B (all day)
Urology/Emergency Medicine, Regency Ballroom
Women's Medical Society of New York State, Versailles Ballroom

Afternoon
Family Practice/Preventive Medicine/Psychiatry, Versailles Terrace
Orthopedic Surgery/General Surgery/Plastic Surgery/Physical Medicine & Rehabilitation/Radiology/Anesthesiology, Georgian Ballroom B
Alcoholism, Regency Ballroom

□

CME CREDITS: Each program will be eligible for CME Category 1 credits on an hour-for-hour basis.

□

Technical & Scientific Exhibits

Advance Registration Form

Complete and return this form to the Medical Society address as indicated below.

1984 Annual CME Assembly, June 29–July 1

SHERATON CENTRE, NEW YORK CITY

PLEASE PRINT

Name ______________________________________
LAST FIRST

Address ______________________________________

City/State/Zip ______________________________________

GENERAL REGISTRATION FEE

Please check category

☐ MSSNY Active Member	$25.00	
☐ MSSNY Life Member	$10.00	Medical Specialty ____________
☐ Non-member physician	$50.00	
☐ Allied Profession	$10.00	

Please check category

- ☐ Nurse
- ☐ Physician Assistant
- ☐ Dentist
- ☐ Lab Technician
- ☐ PT/OT
- ☐ Medical Writer
- ☐ Other (Specify) ____________

NO FEE

- ☐ Speaker
- ☐ Medical Student
- ☐ Medical Assistant
- ☐ Resident/Intern
- ☐ Spouse/Family
- ☐ News Media

MEET THE PROFESSOR

Friday, June 29th only. Fee: $25.00 per session. Please indicate session(s) attending. The six, 1½ hour sessions are limited to 30 persons each.

- ☐ 8:30 a.m. — Stephen Scheidt, M.D.
- ☐ 10:00 a.m. — Richard Gorlin, M.D.
- ☐ 11:30 a.m. — Howard Spiro, M.D.
- ☐ 1:00 p.m. — Eli Friedman, M.D.
- ☐ 2:30 p.m. — Philip Felig, M.D.
- ☐ 4:00 p.m. — Harold Neu, M.D.

(See this issue for subjects to be presented by each Professor)

REMITTANCE

Registration Fee	$ ____________
Meet the Professor session(s)	$ ____________
TOTAL	$ ____________

Please make check payable to:
Medical Society of the State of New York, and return this form with remittance to: Division of Meeting Services, MSSNY, 420 Lakeville Rd., P.O. Box 5404, Lake Success, N.Y. 11042.

Important: Your ID Badge will be held at the MSSNY Registration Desk located in the Exhibition Centre, lower level, Sheraton Centre.

Meet the Professor — JUNE 29th

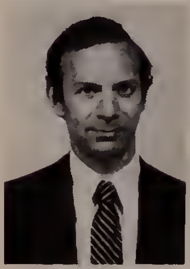
at the Medical Society of the State of New York's Annual CME Assembly, June 29-July 1, Sheraton Centre, New York City. Three sessions, 1½ hours each, will be offered on Friday morning, and three on Friday afternoon. Sessions are limited to 30 attendees each, and there is a $25.00 fee per session. Please see the registration form on the facing page.

Felig

Friedman

Gorlin

Neu


Scheidt

Spiro

Philip Felig, M.D.

Professor of Medicine & Chief of Endocrinology, Yale University School of Medicine, New Haven, Connecticut. This session will deal with newer intensive approaches to the management of diabetes, including self-monitoring of blood glucose, multiple insulin injections and insulin pump therapy.

Eli A. Friedman, M.D.

Professor of Medicine, Chief, Division of Renal Disease, SUNY Downstate Medical Center, Brooklyn, N.Y. Uremia therapy is one of the great successes of this century. There are currently more than 250,000 patients sustained by maintenance hemodialysis, peritoneal dialysis, and renal transplantation. The importance of identification and appropriate preparation of candidates for these therapies is self evident. The major causes of renal failure, its conservative management, and the advantages and problems of each therapeutic option will be considered.

Richard Gorlin, M.D.

Professor & Chairman of Medicine, Mount Sinai Hospital, New York City. The causes of heart failure and certain compensatory mechanisms which are called into play to abate it, in relation to chronic heart failure.

Harold Neu, M.D.

Professor of Medicine & Pharmacology, & Chief, Division of Infectious Diseases, Columbia University College of Physicians & Surgeons, New York City. This lecture will attempt to place all of the cephalosporin antibiotics in perspective so that the practicing physician will know when to use these drugs.

Stephen Scheidt, M.D.

Professor of Clinical Medicine, New York Hospital-Cornell Medical Center, New York City. To update the practicing physician on current knowledge concerning calcium blockers, including new data on arrhythmias, vasospastic angina, chronic stable angina, IHSS, hypertension, and other current or potential indications for their use.

Howard M. Spiro, M.D.

Professor of Medicine, Yale University School of Medicine, New Haven, Connecticut. Update the practicing physician on clinical and technological advances in gastroenterology while keeping the patient's problem as a focus.

Gene Luttenberg

Weekend Sightseeing for the Family

During the CME Assembly, June 29–July 1

SOUTH STREET SEAPORT & LOWER NEW YORK

New York's newest place to be is just a few blocks south of the Brooklyn Bridge, on Manhattan's lower eastern waterfront. It's an 11-block historic district, where in the year 1633, this area was the center of New Amsterdam's mercantile activity. By 1800, its port had surpassed both Boston and Philadelphia's to become the busiest in America. It continued to be an active port for the tall sailing ships until the late nineteenth century when steam ships replaced the sail. Today the area is being preserved and many of the buildings and ships have undergone restoration.

PHOTOS COURTESY N.Y. CONVENTION & VISITORS BUREAU

THE MUSEUM BLOCK

These beautifully restored buildings reflect 200 years of construction and architectural styles. The South Street Seaport Museum office building is believed to be the oldest, constructed in 1797. The Fish Building, built in 1914, is now the Trans-Lux Seaport Theater, with a multi-screen recreation of South Street's heyday. There are 17 shops in Museum Block, including Caswell-Massey, apothecary to George Washington, Blunt's Book & Chart Store which stocks nautical books and charts, the Seaport Gallery which displays ship models, a toy store, apparel shops, and an Italian restaurant.

FULTON MARKET

The original Fulton Market, built in 1822, housed butchers, fish merchants, and produce purveyors. Today, occupying a full block, it has been rebuilt to blend with the architecture of the neighborhood. It offers three exciting floors of restaurants, cafes, and specialty food shops. On the ground floor you can buy coffee, tea, cheese, fresh vegetables and fruits, fresh fish, kitchen accessories, bread and pastry, and you may dine at the sidewalk tables of an American restaurant. On the second level are 22 separate food stalls representing every type of cuisine. On the third floor you will find an elegant restaurant with an outdoor balcony overlooking the seaport.

SCHERMERHORN ROW

Named after the shipowner and merchant, Peter Schermerhorn, this row of late Georgian-Federal commercial buildings was built in 1812. The building provided office space for counting houses, housed seamen, sail makers and other merchants. The row of 12 buildings facing the gray cobblestones of Fulton Street has been cleaned and restored. Today we find an English Pub restaurant, seafood restaurants, marine antiques, and apparel shops.

PIERS 15 AND 16

Here you may view the six moored ships. The four-masted steel bark *Peking* is one of the largest and last sailing ships built for commercial purposes. Built in 1911, she carried nitrate and fertilizer from South America to Europe. The *Wavertree,* an 1884 British full-rigged ship, built for the jute trade between India and Europe, was dismasted off Cape Horn in 1910. Also, you may view the *Ambrose* lightship built in 1907 to mark the entrance to Ambrose Channel in New York Harbor. Other vessels on view are the *Pioneer,* launched as a sloop in 1885 and later restored as a gaff-rigged schooner, plus the *Lettie G. Howard,* a Glaucester schooner built in 1893.

GRAY LINE TOURS

Doctor, we recommend that you bring your family to New York City in June where you may attend meetings at the CME Assembly and also join your family in a tour of the South Street Seaport. The Gray Line offers guided tours of lower New York and the South Street Seaport (Tour #7), and has five hourly departures daily from 9:00 a.m. to 1:00 p.m. In addition to the South Street Seaport, the tour includes views of several squares, including Washington Square, continuing to Chinatown, the Civic Center, the financial and maritime districts, Battery Park, the World Trade Center, and a ride along the East River past the U.N. to Rockefeller Center.

The tour #7 lasts about 5½ hours and departs and returns to the Gray Line terminal located at 8th Avenue and 54th Street, just two blocks from the Sheraton Centre Hotel. The tour price is $19.50, and tickets may be purchased at the theatre/tour desk in the lobby of the Sheraton Centre Hotel.

NEW YORK STATE
JOURNAL OF MEDICINE

May 1984 • Volume 84, Number 5

COMMENTARIES

How can we stop the *Citrobacter?*

Since the first report in 1960, at least 88 cases of *Citrobacter* meningitis have been described.[1-5] This devastating disease is associated with a 70% to 80% incidence of brain abscess and rather extreme resistance to treatment with traditional antimicrobial agents; only 5% of infected patients recover fully.[1] Thus the report of Marcus and colleagues in this issue of the *Journal* of their apparently successful antimicrobial treatment of *C diversus* brain abscesses with the combination of moxalactam and mezlocillin is most welcome. Twelve and 14 months after the disease, two infants treated for brain abscesses appear to be normal. Unfortunately, subtle abnormalities may later become apparent with dramatic repercussions; a Florida court awarded $900,000 to the parents of an infant with a minor neurologic defect five years after the disease.[6]

The first infant in this report developed her disease on the fifth day of life—"early onset" disease.[1] The source is unknown; unlike group B streptococcal disease, no maternal-child transmission has been documented. The second case, "late onset" disease, almost certainly was nosocomial, presumably from a reservoir of stool colonization in the nursery. Cases were limited to the first two months of life, confirming earlier reports.[1]

The apparent cures cannot yet be embraced as triumphs of "simple medical therapy." Even diagnosis is difficult. Counterimmunoelectrophoresis does not detect the *C diversus* antigen, and the first infant's initial sample of spinal fluid was normal. Both infants were hospitalized for two months. Convulsive disorders, *Candida* diaper rash, thrush, hydrocephalus, intracerebral hemorrhage, and two months of intravenous cannulation were all consequences of the illnesses. Moreover, one patient required placement and adjustment of a ventriculoperitoneal shunt. Perhaps early surgical drainage of the brain abscesses might have hastened their resolution and prevented some of the complications.

Although moxalactam was used by these authors and by the Third Neonatal Meningitis Cooperative Study Group, cefotaxime, cefoperazone, ceftizoxime, ceftriaxone, cefmenoxime, or ceftazidime—having similar in vitro activity against *C diversus*—may be effective, with fewer complications.[7] Mezlocillin alone may have been sufficient. Future studies should compare the ureidopenicillins, the new cephalosporins, and combination drug therapy in the treatment of Gram-negative bacillary meningitis.

Why is the organism so virulent? After two decades very little is understood about the pathogenesis of *C diversus* meningitis, and why it attacks apparently healthy infants. The organism also causes necrosis of lung,[8] bone,[8] skin,[9] and kidney[10] in adults, but rarely causes meningitis in the adult population. It does not produce IgA protease, nor is the serotype or biotype found in isolates causing meningitis unique to those strains. Although serotype d is the most common meningitic strain, recent outbreaks in Missouri and Maryland were caused by serotype e, and type a has caused sporadic cases.

In the study of outbreaks, the epidemiologist divides reports of infection into two categories: disease, a disability caused by the presence and multiplication of the organism; and colonization, generally a harmless coexistence of bacteria and human.[11] The latter case is important because the patient remains a reservoir of the organism and may allow transmission of the organism to other patients, who in turn may develop colonization or disease. In previous epidemics, disease-to-colonization ratios have ranged from 4% to 12%.[4,12,13] Thus hospitals have treated patients who are merely colonized for fear that these patients would become ill or would transmit the organism to someone else. Some hospitals have treated these patients with trimethoprim-sulfamethoxazole or cephalexin, some have placed the patients in isolation and others have done both.

A few hospitals have been plagued by indolent epidemics that have lasted up to four years.[1] Does this mean that hospitals that have had patients with *Citrobacter* meningitis and have evidence of persistent colonization in the nursery should continue isolation precautions indefinitely? Although colonization is assumed to be a risk factor for the development of the disease, studies of epidemics have not actually proved that supposition. Unfortunately, the epidemic is detected first, and then surveys of colonization are made. Colonized patients rarely develop meningitis, even after a year of observation as in this outbreak. Noble though the attempts to control colonization may be, they may be useless gestures of securing the barn after escape of the horses. On the other hand, they may well prevent additional cases of meningitis by reducing the total amount of colonization and thus avoiding the critical disease-to-colonization ratio.

Outbreaks can be expensive in terms of laboratory supplies and medical manpower; one estimate was $110,000.[12] Marcus conducted weekly culture prevalence surveys within the nursery for 11 weeks, instituted a strict cohort system, and maintained heightened awareness during the 15 months described after the onset of the outbreak. No doubt, extensive discussions were held within the hospital, staff were rearranged, infection control personnel were diverted from other necessary activities, and families worried, transferred their children, or did both.

Little hope exists for the future. Although *C diversus* accounts for 1.3% of cases of neonatal meningitis,[1] no vaccines are expected soon. Thus, hospitals that encounter cases of meningitis caused by *C diversus* biotypes d or e should implement infection control measures immediately. Although no outbreaks of disease caused by biotype a have been described, such cases should warrant caution. Measures should include emphasis on handwashing, possibly with gloving by personnel; immediate culture prevalence surveys (the rectum generally provides a higher yield for identification); institution of strict cohorts of patients and personnel that will not be violated for the duration of the outbreak. (This may entail enormous burdens on the staff, but personnel may carry the infection for several days after leaving the hospital[12]); aggressive treatment of ill infants in the fashion reported by Marcus et al; considering outside epidemiologic assistance; and saving the organism for further research. Centers in the United States, Great Britain, and Israel maintain an active interest in the disease and welcome submission of strains. Until the epidemiology of *Citrobacter* meningitis can be unraveled, it will remain a threat to our nurseries.

DONALD R. GRAHAM, MD
Chief
Division of Infectious Diseases
Springfield Clinic
Springfield, Illinois 62708

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Legionella and Legionnaires' Disease: "through a glass darkly"

It is one thing to suspect or to have some evidence that a specific microorganism is associated with a disease and quite another to establish unequivocal proof of a specific causal relationship between a microorganism and a given disease. It is even more difficult to determine the exact epidemiologic role of a microorganism if the agent is widespread in nature and frequently found as an environmental isolate not associated with disease. Determining the significance of environmental isolates of *Legionella* and its relationship to Legionnaires' disease has proven to be a case in point.

Following the Philadelphia outbreak, *Legionella* was felt to be a primary pathogen. Initially, lack of available culture media and precautions recommended to avoid laboratory transmission of disease resulted in few reported environmental isolates. However, during the past seven years it has become clear that *Legionella* is widely distributed in nature as part of the natural aquatic environment and is frequently isolated from sources not associated with clinical illness.[1,2] Environmental isolates have been recovered in association with some outbreaks, but a cause and effect relationship can not be concluded. In the United Kingdom, although 36 of 54 water systems of hospitals and large buildings were found to contain *Legionella*, only four facilities reported cases of Legionnaires' disease.[3] Six of 31 hospitals and hotels from which *Legionella* was isolated in the United States reported cases of Legionnaires' disease.[4] Results of an epidemiologic study, associated with Legionnaires' disease in a gravedigger, which appears in this issue of the *Journal*, provides additional evidence that environmental isolates may not be associated with clinical illness. In this case, Legionnaires' disease was due to *L pneumophila*, whereas cultures from the graveyard soil revealed isolates of a serologically distinct strain, *L micdadei*.

Diagnosing legionella infection (Legionnaires' disease) has proven to be a difficult task. Lack of standardization of laboratory criteria required to confirm clinical diagnoses of Legionnaires' disease has resulted in uncertainty of clinical and epidemiologic data. Enthusiasm associated with the discovery of a new disease agent and the lack of a specific diagnostic test has resulted in incriminating *Legionella* in diseases ranging from Fort Bragg fever to sudden infant death syndrome.[5,6] Fort Bragg fever is a classic example of an illness being misdiagnosed as Legionnaires' disease. There is clear proof that Fort Bragg fever, a seasonal, self-limiting, febrile disease that occurred in outbreak form in 1942 and 1943 was caused by *Leptospira autumnalis*.[7–9] Although a rickettsia-like agent, now classified as *L micdadei*, was isolated from a guinea pig during the investigation of the 1943 outbreak, there was no significant antibody response in human cases to indicate infection had occurred.[8] It was subsequently determined that the agent was enzootic in the guinea pig colony and "bore no relation to Fort Bragg fever in human beings."[9] Despite overwhelming evidence that Fort Bragg fever was a form of leptospirosis, the medical literature now indicates that signs and symptoms seen in Fort Bragg fever may be caused by *Legionella*.[5,10,11] The consequences of accepting diagnosis based on uncertain proof confounds our understanding of the epidemiology and pathogenesis of the illness and results in delay in formulating appropriate recommendations for treatment and prevention.

Widespread distribution of *Legionella* and the frequency with which antibodies to them are found indicate that frequent exposure occurs.[12–15] However, only a small number of those exposed acquire overt infection. It is difficult to explain the broad spectrum of disease associated with *Legionella*. Clinical and epidemiologic features of legionella infection in immunocompromised hosts are consistent with our understanding of opportunistic infections. Why benign, self-limiting disease occurred in 95% of healthy employees in one outbreak,[16] fatal pneumonia in previously healthy persons in a second outbreak,[17] yet in a third outbreak cases occurred as opportunistic pneumonia in patients with host defense abnormalities[18] cannot be explained with our current knowledge of the pathogenesis of Legionnaires' disease.

What should we do about *Legionella?* Obviously, when *Legionella* is associated with clinical illness, antibiotic therapy is required. Under most circumstances diagnosis is suspected from clinical findings of atypical pneumonia or of pneumonia in immunocompromised patients. In these clinical settings, empiric therapy with erythromycin should be considered as part of the antibiotic regimen until results of cultures, direct fluorescent antibody tests and serologic tests are known. It is more difficult to decide what to do about *Legionella* in the absence of clinical illness. A prudent and practical approach is to determine the incidence of nosocomial *Legionella* pneumonia in the institution, with emphasis on evaluation of immunocompromised patients. Commercially-available material for cultures, direct fluorescent antibody testing and serologic testing will allow hospitals to identify endemic or epidemic disease. Outbreaks of *Legionella* pneumonia should be investigated for the possibility of the *Legionella* contaminating the water supply and, if a source is discovered, treatment in an attempt to eliminate the potential source may be beneficial.[19–21] To perform surveillance in institutions *without* Legionnaires' disease leads to the dilemma of what to do if the organism is recovered. The high cost and limited success of decontaminating all known environmental reservoirs makes it difficult to sanction in the absence of disease. Final recommendations to prevent Legionnaires' disease will require a more thorough understanding of factors that influence the virulence of the organism and a better understanding of the pathogenesis of the disease.

GARY L. LATTIMER, MD
Chief, Infectious Diseases
The Williamsport Hospital
Divine Providence Hospital
Williamsport, PA 17701

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Resistance to 1,25-dihydroxyvitamin D in hypoparathyroidism: an enigma

Until the various factors contributing to the regulation of the vitamin D-endocrine system were fully appreciated, the variable response of patients with hypoparathyroidism to vitamin D_2 or dihydrotachysterol (DHT) was puzzling to the clinician. The hepatic hydroxylation of vitamin D_2 (plant origin) or vitamin D_3 (mammalian origin) to 25-hydroxyvitamin D (25(OH)D) is followed by a further hydroxylation at the 1-alpha position which takes place in the kidney.[1,2] This latter conversion to 1,25-dihydroxyvitamin D ($1,25(OH)_2D$ or calcitriol) is regulated, at least in part, by parathyroid hormone (PTH). Calcitriol is the most active metabolite with regard to intestinal calcium absorption.[1,2] Thus, the hypoparathyroid patient, lacking PTH, will have reduced conversion of 25(OH)D to calcitriol[3] and will develop reduced serum total and ionized calcium concentrations. The therapeutic use of exogenous calcitriol bypasses this block brought about by hypoparathyroidism and emerges as a logical means of correcting the hypocalcemia typical of this disorder.[4] Calcitriol in "physiologic" doses (0.5 to 2.0 μg) restores serum calcium values to normal and, thus, high doses (1.25 mg or more) of the parent vitamin D compound are unnecessary in the treatment of hypoparathyroidism.

Although most patients with hypoparathyroidism respond to 1.25 to 2.5 mg of vitamin D_2 or 0.8 to 1.6 mg of DHT daily, some patients are "resistant" to these doses of vitamin D.[5] Resistance is a clinical state wherein patients require astonishing doses of vitamin D, often as high as 1 to 2 million units (25 to 50 mg) daily, in order to overcome hypocalcemia. Resistance has been encountered in all forms of hypoparathyroidism—idiopathic, that associated with mucocutaneous candidiasis, pseudohypoparathyroidism, the DiGeorge syndrome (an embryonic failure of descent of the III and IV pharyngeal pouches), and that following surgery. Sometimes patients with hypoparathyroidism will respond to one form of vitamin D but not to others.[5–8] Moreover, resistance may result from other confounding factors, such as poor compliance, high dietary oxalate and phosphate (which bind calcium in the intestine), steatorrhea causing fat-soluble vitamin malabsorption, and pregnancy or lactation when the fetus places unusual demands for calcium on the mother.[6] Magnesium deficiency can be accompanied by hypocalcemia, since magnesium is necessary for PTH secretion[9] and for the stimulation of bone resorption during hypocalcemia.[10] Although treatment with 25(OH)D or DHT can often be used to overcome resistance, a number of patients have been described who are resistant to all forms of vitamin D.[5,7,8]

With our understanding of the mechanisms of the formation of calcitriol, the initial hope was that resistance to vitamin D would cease to be a problem. More extensive experience suggests that calcitriol can be used with safety and efficacy at doses of 0.01 to 0.1 μg/kg/day in children and 0.25 to 2.0 μg/kg/day in adults[11]; these doses are approximately one thousandth as much as required using vitamin D_2. Nonetheless, resistance to calcitriol has been described in patients with idiopathic hypoparathyroidism[12,13] and, in this issue of the *Journal*, in a patient with post-surgical hypoparathyroidism.[14]

In the case described by Chesney et al,[12] malabsorption of calcitriol could not account for this resistance, since the patient's calcium level did not improve despite receiving 6 μg of calcitriol by intravenous infusion. In addition, no evidence was found for an antibody to free circulating calcitriol or to the calcitriol-binding protein complex. Finally, no additional protein binding peak was found in the serum to account for the high serum calcitriol values after oral or intravenous calcitriol administration. Hence, the reason for resistance to calcitriol was not found. Additional, but as yet unproven, mechanisms may underlie resistance to calcitriol, such as more rapid elimination or inactivation of calcitriol by the kidney or other organs, target organ resistance, abnormal intestinal calcitriol receptors, abnormal processing of calcitriol within the intestinal cell or its nucleus, and impaired formation of the gene product(s) of vitamin D that results in active intestinal calcium absorption.

At present, it is also unclear whether patients with post-surgical hypoparathyroidism require larger[15] or smaller doses[8] of vitamin D to correct their hypocalcemia. Clearly, hypocalcemia will be easier to treat if some level of PTH is circulating that can function to resorb bone, thereby raising extracellular calcium concentrations.[5,7,8]

Resistance to calcitriol is an enigma, one which will require careful clinical investigation and new ideas about the role of vitamin D and PTH in the maintenance of normocalcemia.

RUSSELL W. CHESNEY, MD
Professor of Pediatrics
University of Wisconsin
Center for Health Sciences
Madison, WI 53792

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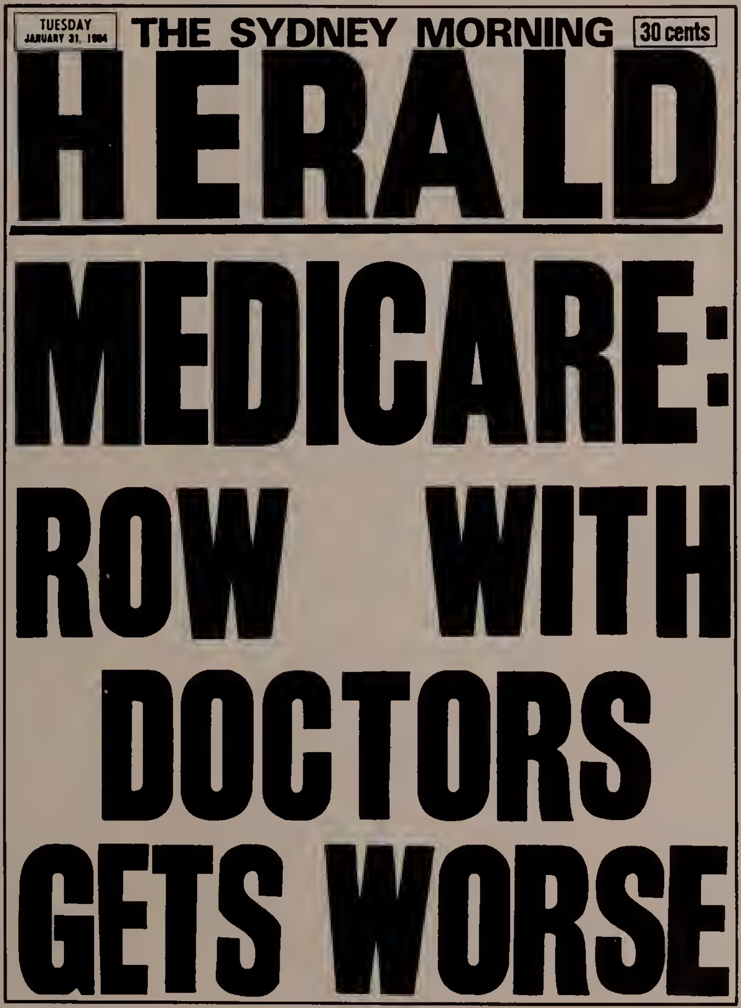

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IT CAN'T HAPPEN HERE, OR CAN IT . . .?

In a detailed series of articles in NYJ News Features (pp 262–269), correspondent Calvin Miller, PhD examines the looming Medicare crisis in Australia.

Address correspondence to Editor, New York State Journal of Medicine, *420 Lakeville Road, Lake Success, NY 11042. Letters should be typed double-spaced and include the signature, academic degree, professional affiliation, and address of each author. Preference is given to letters not exceeding 450 words, and every effort will be made to assure prompt publication. All letters are personally acknowledged by the Editor.*

Over-diagnosis of anorexia nervosa?

TO THE EDITOR: The letter, "Anorexia nervosa in a patient with juvenile diabetes" by Daniel Hardoff, MD, et al (*NY State J Med* 1984; 84:61) prompts this response.

The authors describe an adolescent girl who had become preoccupied with her weight, increased her physical activity, became more withdrawn and isolated herself from peers. Over an eight-month period her weight decreased from 90 lb to 70 lb. She also became amenorrheic and was subsequently hospitalized.

This description is not sufficient for a diagnosis of anorexia nervosa. In recent times the diagnosis of anorexia nervosa has flourished. In my experience a significant number of girls and young women who have been so diagnosed by professionals, and themselves, are not suffering from this disorder. I do not wish to elaborate on the criteria for diagnosis, but among the symptoms should be a very strong fear of becoming obese which persists in the face of losing weight, and a marked disturbance of body image, often of delusional proportion.

That which is described in the letter to the *Journal* can be applicable to a young person with severe depression, identity crisis, or a schizoid or schizophrenic disorder, especially in the early phases of this psychosis.

Recently, the diagnosis of another eating disorder, bulimia, has come to the physician's attention in greater numbers. This too has the tendency of being overdiagnosed. I urge all physicians to read the succinct article in the February 1984 issue of *MD Magazine* on bulimia.[1]

My concern is that physicians may be too quick to diagnosis anorexia nervosa or bulimia as the primary illness when it is not.

IRVING J. FARBER, MD
144-30 Coolidge Ave
Jamaica, NY 11435

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[1] Groh GW: You've come a long way, bulimia. *MD Magazine* 1984; 28:30-34.

In reply: Dr Farber's comments are well taken. Indeed patients with symptoms of anorexia nervosa may exhibit depression, identity crisis or a schizophrenic disorder. We strongly believe, however, that the patient described fits the diagnostic criteria for anorexia nervosa as described by Feighner et al.[1] The patient did indeed have a distorted body image, a fear of becoming obese, hyperactivity, bradycardia, profound weight loss and an enjoyment of losing weight. In another institution she refused to eat despite admonitions, reassurance or threats, and continued to lose weight while under medical and psychiatric care.

The patient eventually did respond to a behavior modification program that has been successful in other patients with anorexia. We believe that although symptoms of anorexia nervosa may be present with other primary psychiatric illnesses, this condition may be but one manifestation of an eating disorder which may include obesity, bulimia, and food avoidance in a continuum of pathology. The patient, now at a normal body weight, continues to have a distorted body image and perceives herself as being fat.

DANIEL HARDOFF, MD
I. RONALD SHENKER, MD
MICHAEL NUSSBAUM, MD
Department of Pediatrics
Long Island Jewish-
Hillside Medical Center
New Hyde Park, NY 10042

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Under-diagnosis of child abuse?

TO THE EDITOR: In the commentary by Daniel Kessler, MD and Francine Siegel-Stein, MD, titled "Retinal hemorrhage, meningitis, and child abuse" (*NY State J Med* 1984; 84:59-60) the authors draw large conclusions from a small data base. These generalities need clarification and correction. They raise critical issues that require more thorough examination and presentation.

With the statement that "it is often impossible to make the diagnosis of child abuse and neglect with any certainty," they overlook the fact that the International Classification of Diseases recognizes the Battered Child Syndrome[1] (E 967) and the Child Maltreatment Syndrome[2] (999.5). These established medical classifications are almost a decade old. The article leaves the impression that lack of knowledge is the reason physicians lack "certainty" in making these diagnoses. Physicians' lack of recognition and often reluctance to get involved and to report suspected child abuse and neglect are more honest and realistic explanations.

Indeed, the commentary promotes such uncertainty that it could easily encourage physicians to avoid their statutory obligation[3] to report suspected child abuse and neglect to the local child protective agency: "The familiar model of identifying (labeling) and reporting (punishing) must be discarded as inadequate," the commentary advises. It further suggests that pediatricians are better able to handle abuse and neglect cases than child protective agencies: "They [pediatricians] can prevent the gaps in services that may occur when many disciplines are involved." These statements, and others like them in the commentary, are unsubstantiated assertions based on an ideological predilection, not on a reasoned understanding of the concept and practice of protective services which has evolved during the last 100 years.

The article overlooks the modern conception of child protective programs as time-limited crisis services that assess the needs of children and parents, obtain the necessary treatment services for them, and monitor the implementation of treatment plans. An effective child protective service does indeed include those functions that the authors say are not a part of its responsibilities, namely, "long-term management" of the coordinated efforts of several disciplines. There is extensive literature[4] on protective services, including standards that delineate these tasks as part of the duties of a protective agency. The authors appear to be unaware of these publications as well as the New York State law that mandates protective agencies to perform the tasks. Section 424.12 of the State Social Services Law provides:

> Each child protective service shall . . . coordinate, provide or arrange for and monitor, as authorized by the social services law, the family court act and by this title, rehabilitative services for children and their families on a voluntary basis or under a final or intermediate order of the family court.[5]

We do not claim that all child protective services programs meet all good practice standards, but there is no basis for assuming, as the commentary asserts, that pediatricians can do better than protective agencies in preventing gaps in service. Unless pediatricians are going to surrender a large part of their practice time—and income producing time—to performing this social work task, they are likely to do a disservice to families and children under their care if they attempt to assume this function.

Pediatricians must find effective ways of advocating improvement within child protective service agencies, rather than attempting to establish parallel or competing programs of their own. Working in collaboration with these programs is a better way for pediatricians to safeguard the health and welfare of children and families who deserve our best.

VINCENT J. FONTANA, MD
Medical Director
NY Foundling Hospital
1175 Third Ave
New York, NY 10021

JOSE D. ALFARO
Coordinator
Mayor's Task Force on
Child Abuse and Neglect
1175 Third Ave
New York, NY 10021

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4. See for example: *Federal Standards for Child Abuse and Neglect Prevention and Treatment Programs and Projects*, National Center on Child Abuse and Neglect, US Dept of Health, Education and Welfare, Washington, DC, March 1978; *A Guide to the Delivery of Child Protective Services*, American Public Welfare Association, Washington, DC, September 1981; *Child Welfare League of America Standards for Child Protection, Revised*, Child Welfare League of America, New York, NY, 1978.
5. *McKinney's Consolidated Laws of New York, Annotated, Book 52A, Social Services Law*, West Publishing Co, St. Paul, MN, 1976.

In reply: It seems clear to us that the mere existence of a diagnostic category does not make it easier to make a diagnosis, especially when the definition of child abuse implies the heavily emotion-laden concepts of "willful infliction of injury" and "intent to harm." The correspondents' comment on our assertion about the imprecision of the current nomenclature is taken out of context. At no time did we imply that any lack of "certainty" in making the diagnosis is due simply to a lack of knowledge, although it is a well-established clinical dictum that you find what you look for and you look for what you know. While it is true that a lack of recognition and a reluctance to get involved in child abuse are important factors in physician underreporting, there is growing evidence that the task becomes easier when the social distance between provider and client increases, a fact which we believe deserves wider recognition.[1-4]

If an impression was given to readers that we are encouraging physicians not to report cases of child abuse and neglect but to "go it alone," or that physicians can do it better than social workers by setting up "parallel or competing programs of their own," then we apologize and indeed are thankful to Dr Fontana and Mr Alfaro and the *Journal* for allowing us this opportunity to set the record straight. This was certainly not the tone set in the first half of the commentary and may have resulted inadvertently from our own editing.

However, to imply that pediatricians do not have a role to play in the identification, assessment, treatment, and—perhaps most importantly—the prevention of child abuse, is to deny reality and a growing professional literature.[5-7] Traditionally, the training of physicians and other health care professionals has focused narrowly on the biological aspects of disease and has only recently acknowledged the importance of environmental and social determinants of illness. To ignore these areas of practice is to ignore the needs of our patients and their families.[8]

In essence, we believe that the correspondents' comments on the child protective system miss the point. The mere existence of professional standards in the midst of limited support for professionals and families alike does not prevent the deaths of innocent children. This was clearly shown in the recent *Report on the Preliminary Study of Child Fatalities in New York City* released under Dr Fontana's auspices. The challenge to us *all* is to translate the rhetoric into action on behalf of the children of New York. In this endeavor, we support their call for collaborative efforts between all agencies, public and private, that labor on behalf of children. This is the guiding principle of our own multidisciplinary program and indeed is the basis for Dr Fontana's own work which serves as a model for us all.[9]

DANIEL B. KESSLER, MD
FRANCINE M. SIEGEL-STEIN, MD
The Carl C. Icahn Program
for the Prevention of Child Abuse
The New York Hospital-
Cornell Medical Center
525 East 68 Street
New York, NY 10021

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The role of closed pleural biopsy in suspected malignant effusions

TO THE EDITOR: Studies on the use of closed pleural biopsy in the diagnosis of malignant pleural effusions have a specified diagnostic accuracy ranging from 48% to 70%.[1,2] Contemporary methods have increased the yield of pleural fluid cytology.[3] The exact role of closed pleural biopsy in patients with positive or suspected-positive pleural fluid findings is becoming less clear. It has been recommended that concomitant thoracentesis and pleural biopsy be

Table I. Correlation of Results of Closed Pleural Biopsy and Pleural Fluid Findings in 19 Patients with Malignant Pleural Effusions

Cytologic Results (No.)	Closed Pleural Biopsy (No.)
Adenocarcinoma (13)	Confirmed diagnosis of adenocarcinoma (5) Undifferentiated carcinoma (1) Changed diagnosis from adenocarcinoma to oat cell carcinoma (1) Negative normal pleura (6)
Squamous cell carcinoma (1)	Confirmed diagnosis of squamous cell carcinoma (1)
Positive for malignant cells (5) cell type indeterminate	Chronic lymphocytic leukemia (1) Large cell carcinoma (1) Oat cell carcinoma (1) Negative normal pleura (2)

performed in order to maximize the diagnostic yield.[4,5] However, such an approach may result in redundant information when cytologic findings from pleural fluid can determine a diagnosis. A question therefore arises as to the need for routine pleural biopsy in patients with suspected malignant effusions when thoracentesis is performed.

To further clarify the role of closed pleural biopsy we reviewed the results of cytologic studies and concurrent closed pleural biopsy in 30 patients with either positive or suspected-positive pleural fluid findings. In each patient the cytologic results were compared to those of pleural biopsy to determine what contribution, if any, pleural biopsy made to the final diagnosis. In 19 patients the pleural fluid findings were positive for malignant cells, and in 11 patients they were suspicious. In the patients who had positive cytologic results, we found that the pleural biopsies confirmed the results in six patients, changed the diagnosis in one patient (adenocarcinoma to oat cell carcinoma), and clarified the diagnosis in three patients in whom the cytologic findings showed malignant cells of indeterminate cell type. One patient's closed pleural biopsy showed undifferentiated carcinoma while the corresponding cytologic analysis showed adenocarcinoma. In the remaining eight patients whose pleural fluid contained malignant cells, the corresponding pleural biopsies showed normal pleura. These results are summarized in Table I. In the 11 patients with suspected-positive pleural fluid findings, the pleural biopsies provided evidence of malignancy in four (36%).

These data suggest that in patients with suspected malignant pleural effusions, a thoracentesis for qualitative and cytologic analysis should be performed without a concurrent pleural biopsy. If malignant cells of a specific cell type are found on cytologic analysis, then the patient may be spared an unnecessary pleural biopsy. If the initial pleural fluid findings yield malignant cells of indeterminate cell type, then a closed pleural biopsy should be performed to establish the cell type. When suspicious cells are found on cytologic analysis, a closed pleural biopsy is indicated to document the presence and cell type of the suspected malignancy. Finally, in patients suspected of having a pleural malignancy even though the cytologic results are noncontributory, closed pleural biopsy, thoracoscopy and biopsy, or open pleural biopsy may be needed to clarify the diagnosis.

FREDERICK A. BEVELAQUA, MD
CONRADO ARANDA, MD
WALFREDO J. LEON, MD
New York University
Medical Center
530 First Ave
New York, NY 10016

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Limp in a child associated with *Yersinia enterocolitica* infection

TO THE EDITOR: Innumerable causes of limp in children have been described. These range in severity from a pebble in a shoe to pyarthrosis, osteomyelitis, and malignant neoplasms.

Bowel disease is frequently associated with joint symptoms. Ulcerative colitis, regional enteritis, and infections of the bowel such as *Salmonella*, *Shigella*, and *Brucella* can cause arthritis and arthralgias.[1]

Our patient presented with a limp, fever, and diarrhea. Stool cultures grew *Yersinia enterocolitica.*

Case report. A 17-month-old boy of Puerto Rican extraction was hospitalized for fever, diarrhea, and a limp. The fever and diarrhea started two days prior to admission. The patient was having four to six watery, non-bloody stools a day. The limp started on the day of admission.

The patient was born in New York City and had not traveled out of the region. None of the other family members was ill. There were no animals in the house.

On admission, temperature was 102°F, pulse rate 148/min, and respiratory rate 32/min. The patient held his right leg in a flexed position and would not bear weight on that leg. There was resistance to passive motion of the leg. Hip abduction was 50 degrees and hip flexion was 80 degrees. There was no swelling, warmth, or redness of the joints. The rest of the physical examination was within normal limits. A slit lamp examination was not performed.

Laboratory data showed a hematocrit value of 32.8%, WBC 21,000/mm^3, and a sedimentation rate of 56 mm/hr (Westergren). Laboratory tests that yielded normal results included urinalysis, serum electrolytes, spinal fluid, antistreptolysin O (ASO) titer, rheumatoid factor, antinuclear antibody (ANA), tuberculin test, and cultures of the throat, urine, blood, and spinal fluid.

Roentgenograms of the chest, lumbosacral spine, pelvis, hips, legs, and feet showed no abnormalities. Bone scan and gallium scan were within normal limits. Stool culture was positive for *Yersinia enterocolitica*, serotype 3. The patient expressed human leukocyte antigen type B27.

Therapy with trimethoprim-sulfamethoxazole was started. Within two days, diarrhea and fever stopped. The patient started walking and the gait became normal over several days. Six months after discharge, the patient had no signs or symptoms of joint involvement, and his sedimentation rate was normal.

Discussion. Yersinia enterocolitica is a gram-negative rod that was first identified as a pathogen in upstate New York in 1933; the organism is known to be endemic to New York.[2] Person-to-person, animal-to-human, food-borne transmissions, and infection from contaminated water have been described.[3] Dogs have been implicated as a source of *Yersinia enterocolitica* infection.[4]

Cultures are most frequently positive when obtained early in the course of the illness. They are rarely positive when obtained more than one month after the onset of symptoms.[1]

Children with *Yersinia enterocolitica* infection frequently have high fever, occasionally causing febrile convulsions. Headaches are a common complaint.[5] Infants usually have diarrhea, frequently with blood or mucus. In older children, abdominal pain with mesenteric lymphadenitis or terminal ileitis, occasionally mimicking appendicitis, is the most common presentation.[6]

Arthritis or arthralgias, or both, have also been reported with *Yersinia enterocolitica* infection. Although arthritis appears in 50 percent of adults with *Yersinia enterocolitica* infection, only about 5 percent of children with this infection will have associated joint symptoms.[7] Patients with HLA type B 27 may be predisposed to arthritic manifestations of *Yersinia enterocolitica*.[8] The mechanism of reactive arthritis in these patients is not clear. Reactive arthritis may be the result of the release of immunologic mediators into the circulation. There is no clear evidence that microorganisms or antigens from the primary infection are deposited in the synovium.[9]

Yersinia enterocolitica is usually susceptible to trimethoprimsulfamethoxazole therapy. It is also sensitive to chloramphenicol, tetracycline, colistin, gentamicin, and kanamycin.[1] Ampicillin resistance is quite common.[7]

A child with a limp and diarrhea should be investigated for *Yersinia enterocolitica* infection. Early diagnosis may save the child from many unnecessary laboratory tests and radiation exposure.

STUART BEREZIN, MD
LEONARD J. NEWMAN, MD
EDWARD WASSERMAN, MD
Section of Pediatric
Gastroenterology and Nutrition
New York Medical College
Westchester County Medical Center
Valhalla, NY 10595

1. Jacobs JC: *Yersinia enterocolitica* arthritis. *Pediatrics* 1975; 2:236-238.
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Report of a pilot project on the outpatient treatment of alcohol problems

TO THE EDITOR: Counselling for alcoholism is frequently done in facilities that deal with addiction or in psychiatrists' offices. Since such programs are limited, we wondered if such counselling could be done in an internist's office, an additional treatment resource. Accordingly, we, a physician who has long had an interest in alcoholism and a Certified Alcoholism Counsellor (CAC), started a pilot project for the outpatient counselling of alcoholism in the former's office.

Between March 1981 and October 1982, 22 patients were seen by one or both of us. The patients were referred from judges, clergymen, self-help groups, and medical patients being followed for other diseases. There were nine women and 13 men. Their median age was 44 years (range 15 to 75 years). Twenty-one were white; one, black. They were all middle or upper middle class and resided in one of two suburbs of New York City. Fifteen were drinking when first seen (10 alcoholics, those addicted physically or psychologically to alcohol; four problem drinkers, those not addicted but for whom alcohol caused severe personal, physical, social or employment problems; and one social drinker), seven were recovering alcoholics (those who had stopped drinking before beginning counselling), and, somewhat to our surprise, we were consulted by 15 relatives of alcoholics (13 women and two men; 11 belonged to Alanon). Median follow-up of all 37 patients is eight months. Of the drinking alcoholics, seven (70%) have stopped drinking (and are considered treatment successes) and three (30%) are either drinking or are lost to follow-up (and are considered failures). Only one (25%) of the problem drinkers became abstinent and was a success; three (75%) continued to drink and were considered failures. None of these patients underwent concurrent treatment, including that of Alcoholics Anonymous, while in our care. All seven (100%) of the recovering alcoholics benefited from counselling. Thirteen (87%) of the relatives of alcoholics also were helped; two (13%) were not. Overall, 27 patients (77%) were aided by us and 8 (23%) were not or were lost to follow-up. (The social drinker was not considered helped or not helped.) We conclude that treatment for alcoholic problems can be successfully accomplished in an internist's office, and we recommend our methods to others for verification and for comparison with the results of treatment done in counselling facilities.

RICHARD J. LANHAM, MD
Assistant Clinical Professor of Medicine
The Albert Einstein College of Medicine
Bronx, NY 10461

LOU MEISEL, CAC
New York Hospital
Cornell Medical Center
Westchester Division
Alcoholic Treatment Services
White Plains, NY 10605

Malignant schwannoma presenting as an inguinal-scrotal mass

TO THE EDITOR: Tumors of nerve sheath are not common; about 50 percent of them arise in patients with multiple neurofibromatosis.[1] Neurilemoma is the purest example of a Schwann cell tumor or schwannoma. It is essentially benign and has no propensity to malignant transformation.[2,3] Recently we had the opportunity to treat a patient with a large malignant schwannoma arising from a branch of the ilioinguinal nerve in the spermatic cord. It extended into the retroperitoneal space, inferior to the upper third of the left thigh and medial to the left scrotum.

Case report. A 67-year-old black man was admitted to Interfaith Medical Center with a history of progressive swelling of the left inguinoscrotal region of six months' duration. The mass produced no symptoms. The only pertinent physical findings were (1) BP 160/100 mm Hg, (2) soft abdomen without any enlargement of liver or spleen and no evidence of hernia, (3) a large hard mass extending from the left inguinal region to the left upper thigh anteriorly and the left scrotum medially; the mass was fixed, not tender and not pulsatile and the borders were ill-defined, (4) the left testis was not identified, and the penis was retracted, (5) the prostate was not enlarged, and rectal examination disclosed no abnormalities, (6) the peripheral pulses were normal; no edema was present.

With the diagnosis of possible fibrosarcoma, the patient underwent a tumor work-up. Blood count, urinalysis, blood and liver chemistries, prothrombin and partial thromboplastin time. Chest roentgenogram, EKG, liver and spleen scan, bone survey, intravenous pyelogram, proctosigmoidoscopy and barium enema were all within normal limits. Only the femoral angiogram demonstrated a hypervascular, soft tissue mass extending from the retroperitoneal left inguinal region to the thigh with vascular displacement. The venogram showed no obstruction of either the external or the left common iliac vein.

After a complete mechanical and chemical bowel preparation, the mass was approached through a left lower abdominal and left flank "Hockey Stick" type of incision. The peritoneum was not entered but could be dissected and retracted superiorly. The mass appeared to arise from the left spermatic cord at the internal inguinal ring. The tumor was excised along with the left spermatic cord, the scrotum, and the left testis. A muscle-fascial flap was fashioned from the left internal oblique and transversus abdominal muscles to protect the femoral vessels and to close the inlet of the femoral canal. On pathologic examination, the tumor mass measured 20 cm in diameter and weighed 1,500 gm. It was pale and pinkish with a smooth, glistening cut surface. On microscopic examination, a cellular neoplasm was described with abundance of spindle cells and numerous mitoses. The tumor was found to arise within the anatomic compartment of a nerve, and transition was noted between nerve cells and neoplastic cells (Fig 1). After surgery, the patient had a good recovery.

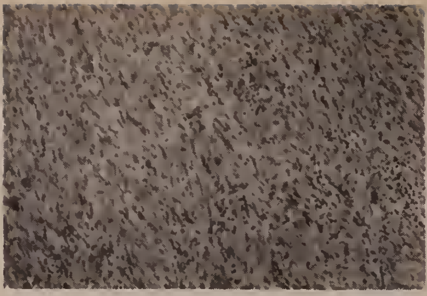

Figure 1. Photomicrograph of malignant schwannoma. Pattern of elongated fusiform cells forming intertwined bands in parallel rows.

Discussion. Malignant schwannomas are composed of Schwann cells derived from the multipotential neural crest. They do not arise from encapsulated neurilemomas but from the more diffuse form represented by the neurofibroma.[3,4] The largest number of cases in which neurogenic tumors were reported was collected by the Memorial Sloan-Kettering Cancer Center (271 cases from 1931 to 1970). All of the tumors reported were classified as neurogenic sarcomas.[3] Half or more of those tumors arose in persons with Von Recklinghausen's disease[1,5] and were found in the back, axilla, neck, and the posterior mediastinum.[3,6,7] The tumors not associated with multiple neurofibromatosis were found in the arm, neck, back, and buttock.

The inguinal region and the retroperitoneum are unusual sites for peripheral malignant schwannomas not associated with neurofibromatosis.[7] The prognosis for patients with malignant tumors of nerve sheath origin is poor, and there is a 70% to 95% mortality rate within three years.[4] Malignant schwannomas are known for frequent local recurrence and also for distant metastases. More malignant than the fibrosarcoma, they spread along lymph spaces in the nerve itself and along perineural and perivascular channels.[8] Involvement of lymph nodes is rare. The treatment of choice is radical excision. Benefits from adjuvant radiotherapy and chemotherapy are questionable and still under evaluation.

ANDRÉ MUZAC, MD
ERNESTO MENDOZA, MD
Interfaith Medical Center
555 Prospect Place
Brooklyn, NY 11238

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CORRECTION

An error was made in the caption for the photographs on p 81 of the article "Henri Dagonet: Pioneer of psychiatric photography" by Aaron H. Esman, MD (*NY State J Med* 1984; 84:79-81). The caption should read as follows: Left, Patients with cretinism and goiter. Center, patients who would fulfill current criteria for mania. Right, "*Lypémanie*," profoundly psychotic cases with multiple hallucinations and delusions of persecution.

Treatment of cervical intraepithelial neoplasia

SHASHIKANT B. LELE, MD, M. STEVEN PIVER, MD, JOSEPH J. BARLOW, MD,
MARY EILEEN MCPHEE, RN

ABSTRACT **Cryotherapy, cone biopsy or hysterectomy was used to treat 98 patients with moderate to severe dysplasia and carcinoma in situ of the cervix. Cryotherapy was administered only after cytologic and biopsy correlation in all patients. None of the patients had a recurrence after a minimum of nine months follow-up. Recurrence within the first nine months of follow-up was noted in two of 35 patients (5.7%) who received cryotherapy, in one of 25 (4%) subjected to cone biopsy, and in none of those who underwent hysterectomy. All recurrences were seen in the carcinoma in situ of the cervix group.**

(NY State J Med 1984; 84:233–235)

INTRODUCTION

The incidence of invasive cervical cancer has shown a steady decline since the introduction and use of Papanicolaou (Pap) cervical smears. More preinvasive and early invasive cervical neoplasia are being detected in areas with active screening programs. In a 1977 study carried out in British Columbia, it was noted that the incidence of cervical intraepithelial neoplasia had doubled in women between the ages of 20 and 30.[1] Hysterectomy, which was the preferred treatment in the past, has been replaced by conservative measures such as cone biopsy, cryotherapy and laser surgery. To avoid the high cost of hospitalization the emphasis has been on outpatient methods of therapy such as cryosurgery and laser therapy. Cryosurgery has been the preferred treatment by many gynecologists in their office practices because of its low cost, ease of administration, and its effectiveness with few side effects. We, at Roswell Park Memorial Institute (RPMI), see patients with intraepithelial neoplasia infrequently, as we are mainly a referral center for the management of invasive cancer. The patients who are referred with preinvasive disease are seen because of difficulty in their diagnosis or because of the patients' choice of coming to a cancer center. This retrospective analysis of three treatment forms in the management of cervical intraepithelial neoplasia was made to determine the efficacy of each form of treatment.

PATIENTS AND METHODS

Ninety-eight patients referred between January 1974 and June 1981 with a diagnosis of either cervical dysplasia, carcinoma in situ or possible invasion, but who were found to have disease confined to the cervical epithelium, are the subject of this report. The patient had a repeat Pap smear and underwent colposcopy examination and biopsy of areas that had an abnormal pattern on colposcopic examination.

Cryotherapy was performed in patients in whom the entire transformation zone was seen, with no extension of disease into the endocervical canal. Other requirements for cryotherapy were a correlation, within one degree, between Pap smear and colposcopic-directed biopsies and a negative endocervical smear. Cryotherapy was performed on 35 patients using the 3 min freeze, 5 min thaw and 3 min freeze technique with the Ohio cryosurgery unit that produced probe temperatures of −70°C to −80°C using nitrous oxide as the refrigerant. Treatment was defined as successful when a cytologic smear was normal three months after therapy. Persistence was defined as an abnormal smear at the end of three months following cryosurgery, and recurrence was determined by one or more normal smears followed by an abnormal smear during the course of follow-up.

Patients were treated with conization of the cervix when there was a disparity between the pap smear diagnosis and the biopsy findings, when the entire transformation zone was not seen on colposcopic examination, or when endocervical curettings were positive. Conization was performed in the operating room under anesthesia using Schiller's or Lugol's iodine stain so as to include Schiller- or Lugol-positive areas in the cone biopsy specimen.

Hysterectomy was performed when there was a suspicion of invasive carcinoma as observed by pap smear or inadequate biopsy or as patients' choice because of age.

RESULTS

Tables I and II show the treatment type, age, type of dysplasia, and the follow-up period in months of the three patient groups. The age range in the cryotherapy group was 18 to 82 years with a median age of 29 years; 22 patients (62.8%) were between the ages of 20 and 30 years. Three patients were lost to follow-up, one after follow-up of 15 months, one after three years of follow-up, and the third after being followed for six years. Persistent disease was found in five patients when the Pap smear was repeated before three months; however, only one of these patients was found to have true persistent disease at three months follow-up, and the remainder of the patients had negative Pap smears. There were two recurrences, one at six months and another at nine months follow-up. Both of these recurrences were seen in the carcinoma in situ group as shown by cytology and later confirmed by cone biopsy, with no recurrences in the dysplasia group of patients.

Cone biopsy was performed in 25 patients. Their ages ranged from 21 to 78 years, with a median age of 31 years; 11 patients (44%) were between the ages of 20 and 30 years. Three patients were lost to follow-up, one after nine months, the second after 18 months, and the

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From the Department of Gynecologic Oncology, Roswell Park Memorial Institute, Buffalo, New York.

Address correspondence to Dr Lele, Associate Chief, Department of Gynecologic Oncology, Roswell Park Memorial Institute, 666 Elm St, Buffalo, NY 14263.

TABLE I. **Treatment versus Patient Age and Type of Dysplasia**

Treatment	Patients (no.)	Median Age (yr)	Age Range (yr)	Mild Dysplasia (no.)	Moderate Dysplasia (no.)	Severe Dysplasia (no.)	Carcinoma in situ (no.)
Cryosurgery	35	29	18–82	0	7	13	15
Cone biopsy	25	31	21–78	0	2	11	12
Hysterectomy	38	41	24–74	0	0	5	33

third patient was lost to follow-up after five years. One recurrence was noted at six months of follow-up. The distribution among patients of dysplasia and carcinoma in situ is given in Table I. Indication for cone biopsy of the cervix was disparity between the pap smear and colposcopic biopsy findings in 17 patients and nonvisualization of the transformation zone in seven patients; one patient elected to have a cone biopsy as her therapy. All the cone biopsy margins were free of disease on entire sectioning of the cervix.

Vaginal or abdominal hysterectomy was performed in 38 patients. Ages ranged from 24 to 74 years, with a median age of 41 years; there were six patients (15.8%) between the ages of 20 and 30 years. Follow-up of these patients is given in Table II. Four patients were lost to follow-up in this group; one was lost to follow-up after being followed for two years, one after four years of follow-up, and two patients after being followed for five and seven years. There was one recurrence that proved to be a new primary carcinoma in the upper vagina when the patient was seen for her 24-month follow-up. Thus, there was no recurrence in this group. The indications for hysterectomy were the patients' ages and by choice in 19 patients. Fifteen patients had a suspicion of invasion on Pap smear. They underwent a cone biopsy with frozen section to rule out invasion, followed by a simple hysterectomy. Two patients had recurrence of dysplasia following conization of the cervix at an outside institution. Two other patients had carcinoma in situ of the cervix associated with invasive vulvar cancer in one patient and carcinoma in situ of the vulva in the other.

DISCUSSION

Cryotherapy continues to be an important method for treating cervical intraepithelial neoplasia. The failure rate varies depending upon the criteria used and the severity of disease. Earlier reports indicated persistence of disease in 8% to 19% of the patients treated. Creasman et al[2] demonstrated that persistence was higher in patients treated with a single freeze method as opposed to those treated with freeze-thaw-refreeze technique, the method used in this series. Persistence is also reported to be higher in patients in whom the lesion extended into the endocervical canal, and in severe dysplasia and carcinoma in situ lesions versus milder dysplasia. Richart et al[3] demonstrated that once the dysplastic lesion is eradicated by cryosurgery, the recurrence rate is acceptable and comparable to that of the conization procedure. The large number of cases recurring in the first two years were a result of diagnostic errors rather than true recurrences. They found no differential risk of recurrence between cervical intraepithelial neoplasia grades 1, 2 and 3. The failure rate following cryotherapy, depending upon the criteria used, is in the range of 10% to 30%.[2–6] Careful follow-up of reliable patients is important. The low rate of recurrence in this series of patients (5.6%) was achieved by adhering to strict criteria before choosing cryotherapy. Our finding of five patients with persistent disease when the Pap smear was repeated before three months, with only one patient showing disease after three months, demonstrates the time period required for repeating the smear following cryotherapy.

Bjerre and co-authors[7] demonstrated that with cone biopsy the recurrence rate of dysplasia was only 0.8% when the cone margins were free of disease, whereas in 13.3% (165 of 1,237 patients) the first smear was positive indicating persistent disease from inadequate therapy. Burghardt and Holzer[8] found a rate of 6.8% for persistent disease in the first year of follow-up in 1,219 patients who underwent cone biopsy and only a 3.4% recurrence rate in follow-up of a year or more. In the same study they found that 634 patients who had negative cone biopsy margins, as shown by step sectioning, had no evidence of persistent disease, and only two of 634 (0.3%) had recurrent disease.[8] The overall recurrence rate of 4% in this series of patients cannot be compared with the rate reported by Burghardt and Holzer because of the smaller patient population. It emphasized, however, that clear margins on cone biopsy should be the most important criteria when this method is chosen as the definitive therapy.

Thirty-eight patients who underwent hysterectomy for severe dysplasia and carcinoma in situ showed no evidence of recurrence. Their median age of 41 years was one of the important reasons for the selection of this treatment as well as the fact that 15 of the 38 patients were referred with a Pap smear showing possible invasive carcinoma cells.

Carbon dioxide laser therapy has been used with success rates comparable to those of other forms of therapy for intraepithelial neoplasia.[9,10] The advantage of this form of therapy is that inflammatory changes in the treated zone are minimal, with less tissue scarring compared to cryotherapy.

TABLE II. **Follow-up of Patients with Dysplasia and Carcinoma in Situ**

Treatment	Follow-Up (months)							Total Number of Patients
	4–12	12–18	18–24	24–36	36–48	48–60	60+	
Cryosurgery	2	5	3	4	5	6	10	35
Cone biopsy	4	7	3	4	3	1	3	25
Hysterectomy	2	3	3	3	3	5	19	38

In conclusion, cryosurgery and laser surgery will continue to be the preferred method of treatment in younger patients with good cytologic, colposcopic, and biopsy correlation. Cone biopsy and hysterectomy should be reserved for patients that are difficult to diagnose due to a nonvisualized transformation zone, positive endocervical biopsy, lack of correlation between the Pap smear and biopsy findings, or a patient who is not reliable for follow-up following cryosurgery or laser surgery.

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An outbreak of influenza A in a nursing home, 1982

LAWRENCE D. BUDNICK, MD, RACHEL L. STRICOF, MPH, FLORENCE ELLIS, RN

ABSTRACT During December 1982, 49 of 81 (60.5%) residents at a skilled nursing facility in New York State experienced influenza-like illness. Nine of 10 acutely ill residents studied had influenza A/Oregon/4/80-like(H3N2) virus isolated from respiratory specimens or serologic evidence of recent influenza A(H3N2) infection, or both. Recent influenza vaccination was 46.6% effective in preventing clinical influenza-like illness, but vaccination one year earlier with the same influenza vaccine offered minimal protection against illness.

(NY State J Med 1984; 84:235-238)

INTRODUCTION

The elderly and individuals with chronic illness have long been know to have the greatest risk of serious illness or death due to influenza,[1] and for people aged 65 years and older, pneumonia and influenza are the fourth leading cause of death.[2] Individuals who are confined to institutions, such as elderly residents of nursing homes, may have an especially high risk of severe consequences due to influenza.[3] Influenza vaccine is strongly recommended for the elderly and for persons with certain chronic medical conditions.[4]

In December 1982, an influenza A outbreak occurred in Nursing Home A (NHA), an 80-bed skilled nursing facility in Waverly, a rural community of about 6,000 persons in south-central New York State. Immediately after the increase in upper respiratory illness was noted, the NHA infection control committee adopted control measures that included cancelling all resident activities, restricting ill residents to their rooms, restricting ill employees from working, restricting visitors with influenza-like symptoms, and limiting admissions. The outbreak was investigated to determine the efficacy of the influenza vaccine used at the nursing home.

METHODS

We reviewed the clinical records of all NHA residents from December 1, 1982 to January 4, 1983. A resident was defined as having had influenza-like illness if, during the period under study, the resident was noted in the record to have had an elevated temperature (either ≥37.8°C (100.0°F) oral or ≥38.0°C (100.4°F) rectal) and at least one of the following symptoms: cough, congestion or sore throat. In addition, we reviewed the hospital records of all residents hospitalized during December 1, 1982 through January 6, 1983, and the postmortem report for the one resident who died during that time and underwent an autopsy.

NHA staff obtained pharyngeal swabs for attempted virus isolation from six of the acutely ill residents. All myxoviruses isolated were propagated in embryonated eggs; antigenic analysis was performed using ferret sera by standard hemagglutination-inhibition (HI) procedures.[5] Acute- and convalescent-phase sera were obtained from six of the residents who had been ill, including two from whom pharyngeal swabs had also been obtained, and were tested for HI antibody titers to influenza viruses A/England/333/80(H1N1), A/Bangkok/1/79(H3N2), B/Singapore/222/79, and B/Singapore/222/79ET at the World Health Organization Collaborating Center for Influenza at the Centers for Disease Control (CDC).[5] Lung tissue from one resident who died was cultured for viruses.

We reviewed the vaccination policies of NHA. The 1982-1983 influenza vaccine contained 15 µg each of A/Brazil/78(H1N1), A/Bangkok/79(H3N2), and B/Singapore/79 hemagglutinin antigens per 0.5 mL and was identical to the 1981-1982 influenza vaccine. The vaccines used were from two lots of one manufacturer's subvirion trivalent influenza vaccine, both of which expired June 30, 1983, and their potencies were determined by the United States Food and Drug Administration Office of Biologics. The calculated rates of vaccine efficacy were based on the attack rates of clinical influenza-like illness among those vaccinated with trivalent influenza vaccine (AR_{vac}) and those not

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From the Influenza Branch, Viral Diseases Division, Center for Infectious Diseases (Dr Budnick), Centers for Disease Control, Atlanta, GA; Bureau of Communicable Disease Control (Ms Stricof), New York State Department of Health, Albany, NY; Tioga General Hospital (Ms Ellis), Waverly, NY.

Address correspondence to Dr Budnick, Epidemic Intelligence Service Officer Special Studies Branch, C-9A, Centers for Disease Control, Atlanta, GA 30333.

vaccinated (AR_{unvac}), with vaccine efficacy (%) = $[(AR_{unvac} - AR_{vac})/AR_{unvac}] \times 100$.

We gave all NHA employees questionnaires concerning influenza-like illness during December 1982. Probable influenza-like illness was defined as having a documented elevated temperature (as defined for residents) and at least one symptom (cough, congestion, sore throat, myalgia, or headache), and possible influenza-like illness was defined as having at least two symptoms (of the five noted above and fever), but no documented elevated temperature. No biological specimens for laboratory analysis were obtained from the employees.

NHA is affiliated with and attached to Hospital A, a 67-bed, acute-care, voluntary hospital, and is 3 miles from Hospital B, a 367-bed regional medical center. We reviewed the emergency room logbooks of Hospitals A and B from November 1, 1982 to January 2, 1983, and the Hospital B virology laboratory logbook from October 1, 1982 to January 5, 1983. All laboratory specimens identified as myxoviruses were sent to CDC, were propagated in embryonated eggs, and underwent antigenic analysis as described above.

Statistical methods used in the analyses of data included Student's t-test, the chi-square test for independent samples, and Fisher's exact test.[6] Two-tailed probability values are reported, and a probability of ≤.05 is considered significant.

RESULTS

Eighty-one residents lived in NHA between December 1, 1982 and January 4, 1983, and 49 (60.5%) had an influenza-like illness (Fig 1). For six residents, the onset of illness occurred sporadically before December 18, when the continuous outbreak began. All residents required skilled nursing care, and they lived in either of two areas in NHA. Influenza-like illness occurred in both areas, with attack rates of 65.9% in the north area and 55.0% in the south area ($P > 0.30$), and the spread of illness was concurrent. Therefore, residents of both areas were considered together.

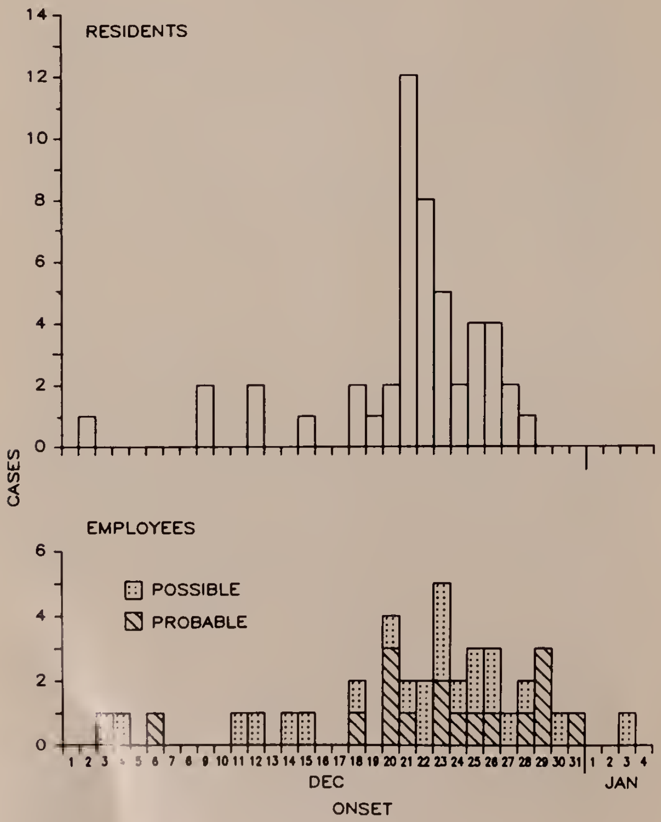

FIGURE 1. Number of nursing home residents and employees with influenza-like illness, by date of onset, New York, December 1, 1982 to January 4, 1983.

Characteristics of the ill and well NHA residents are presented in Table 1. All residents were older than 65 years, except for one 37-year-old women with cerebral palsy. The mean age of the ill women was 87.9 years and of the ill men was 82.7 years, which was not significantly different from the mean ages of the well women and men (84.8 and 84.2 years, respectively). Forty-four (88.9%) of the ill residents were reported to have cough, 37 (75.5%) congestion and 11 (22.4%) sore throats. The mean peak temperature was 38.8°C (101.8°F), and the mean duration of fever was 5.1 days. The clinical findings were not significantly different between the vaccinated and unvaccinated ill residents.

The use of influenza vaccine for residents was promoted by NHA. The social services department requested permission to vaccinate from all residents who were capable of granting informed consent or from a responsible family member for those residents incapable of granting informed consent. Physicians authorized vaccine use for all residents from whom informed consent was obtained. The 1982-1983 influenza vaccines used were of satisfactory potency. In NHA, 55 (67.9%) of the residents were vaccinated with the 1982-1983 influenza vaccine, with 49 (89.0%) of them receiving it in October 1982, and three (5.5%) each in November and December 1982. The attack rate of clinical illness among the unvaccinated residents was 88.5%, and among the vaccinated residents was 47.3%, which was significantly lower ($P < .001$). The calculated rate of vaccine efficacy in preventing clinical illness was 46.6%. Concerning the 1981-1982 influenza vaccine, the attack rates of clinical illness among the unvaccinated and vaccinated residents were 64.4% and 55.5%, respectively, and the calculated rate of vaccine efficacy in preventing clinical illness was 13.8%.

Seven NHA residents were hospitalized. Six had influenza-like illness, of whom four had not received the 1982-1983 influenza vaccine. Three hospitalized and one other resident with influenza-like illness died, for a case-fatality ratio of 8.2%. A postmortem examination of one fatality revealed bilateral hemorrhagic bronchiolitis, but no viruses were isolated from lung tissue cultures. Another hospitalized resident, who did not have antecedent influenza-like illness, died. In comparison, there had been only two deaths in NHA during the previous three months ($.10 > P > .05$). The other three hospitalized residents were all readmitted to NHA after a mean stay of 13 days in Hospital A.

An influenza A/Oregon/4/80-like(H3N2) virus was isolated from cultures taken from all six acutely ill residents tested. Five of the six paired serum specimens demonstrated at least a 4-fold increase in reciprocal antibody titer to influenza A/Bangkok/1/79(H3N2) virus, and there were no changes in the antibody levels to the other viruses tested. Altogether, nine of the 10 ill residents tested had evidence of recent infection with influenza A(H3N2) virus.

Of the 132 NHA employees surveyed, 101 (76.5%) responded. Nineteen (18.8%) of the employees had probable influenza-like illness, and 25 (24.8%) had possible influenza-like illness. For 40 of these ill employees, the date of onset of symptoms was known (Fig 1). Only two (4.5%) of the ill and six (10.5%) of the well employees received 1982-1983 influenza vaccine. The attack rate of influenza-like illness among the nursing staff (52.7%) was significantly greater than that among other employees (32.6%).

In the Hospital A and Hospital B emergency rooms, the daily mean number of visits and the number and percentage of visits for acute respiratory illness increased significantly during the weeks ending December 12 and December 19, respectively (Fig 2).

An influenza A/Oregon/4/80-like(H3N2) virus was isolated from five respiratory specimen cultures at the Hospital B diagnostic virology laboratory in December; none were isolated previously. Three were from NHA residents, one was obtained December 7 from a nine-year-old girl, and one was obtained December 22 from a 49-year-old woman. Both of these ill persons lived in Waverly. Until January, no influenza viruses were obtained from any cultures of respiratory specimens submitted for people from other nearby communities.

DISCUSSION

The outbreak of influenza-like illness at NHA was un-

Table I. Characteristics of Ill and Well Residents in Nursing Home A and Attack Rates, December 1, 1982–January 4, 1983

	Ill Residents		Well Residents		All Residents		Attack Rate
	n	(%)	n	(%)	n	(%)	%
Total	49	(100.0)	32	(100.0)	81	(100.0)	60.5
Sex							
Women	38	(77.6)	27	(84.4)	65	(80.2)	58.5
Men	11	(22.4)	5	(15.6)	16	(19.8)	68.8
Age							
< 65 years old	0	(0.0)	1	(3.1)	1	(1.2)	0.0
65–74 years old	2	(4.1)	4	(12.5)	6	(7.4)	33.3
75–84 years old	15	(30.6)	6	(18.8)	21	(25.9)	71.4
85–94 years old	27	(55.1)	17	(53.1)	44	(54.3)	61.4
≥ 95 years old	5	(10.2)	4	(12.5)	9	(11.1)	55.6
Chronic medical conditions							
Atherosclerotic heart disease	45	(91.8)	26	(81.3)	71	(87.6)	63.4
Anemia	10	(20.4)	8	(25.0)	18	(22.2)	55.6
Pulmonary disease*	12	(24.5)	2	(6.2)	14	(17.3)	85.7
Diabetes mellitus	6	(12.2)	3	(9.4)	9	(11.1)	66.7
Renal disease	2	(4.1)	2	(6.2)	4	(4.9)	50.0
Cancer	1	(2.0)	2	(6.2)	3	(3.7)	33.3
Influenza vaccine immunization history†							
1982 and 1981	12	(24.5)	16	(50.0)	28	(34.6)	42.9
1982, not 1981	14	(28.6)	13	(40.6)	27	(33.3)	53.8
1981, not 1982	8	(16.3)	0	(0.0)	8	(9.9)	100.0
neither 1982 nor 1981	15	(30.6)	3	(9.4)	18	(22.2)	78.9

* Significant difference between ill and well residents ($P < .05$)

† Significant difference between ill and well residents ($P < .01$)

usual because of the high attack rate of clinical illness, especially among those who did not receive the 1982-1983 influenza vaccine. Although a concurrent influenza A and respiratory syncytial virus outbreak has been reported,[7] and the attack rates in this investigation were based on clinical findings of influenza-like illness, the outbreak was apparently due to influenza A/Oregon/4/80-like (H3N2) virus. Evidence of influenza A(H3N2) virus infection was documented in 90% of those tested, who accounted for 18.4% of the ill residents. In the nation as a whole, influenza virus type A(H3N2) was predominant during the 1982-1983 influenza season.[8]

The outbreak was probably a reflection of influenza activity in the community, and the NHA employees probably introduced the virus to the residents. The excess of nurses among the employees with influenza-like illness may represent a greater prevalence of illness among those with greater contact with the residents, or it may represent ascertainment bias, since nurses may be more likely to suspect and report an illness.

Although the continuous outbreak among the residents, which began on December 18 and peaked on December 21, appears to be that of a common source outbreak, no unusual event occurred during the several preceding days. Until December 24, however, the residents did participate in daily activities, including religious services on December 19. The ill and well residents did not differ significantly in any of the characteristics studied, except for the prevalence of chronic pulmonary disease and the history of influenza vaccination.

Recent influenza vaccination was 46.6% effective in preventing clinical influenza-like illness, but the same influenza vaccine when given one year earlier apparently offered minimal protection against the current outbreak. This may indicate a temporal limitation to the protection offered by available influenza vaccines. In addition, those who received the 1981-1982 vaccine may have been more debilitated or chronically ill for a longer time than those who did not receive it. Also, the record of receiving the 1981-1982 vaccine was less accurate than the record of receiving the 1982-1983 vaccine because, as in other influenza A

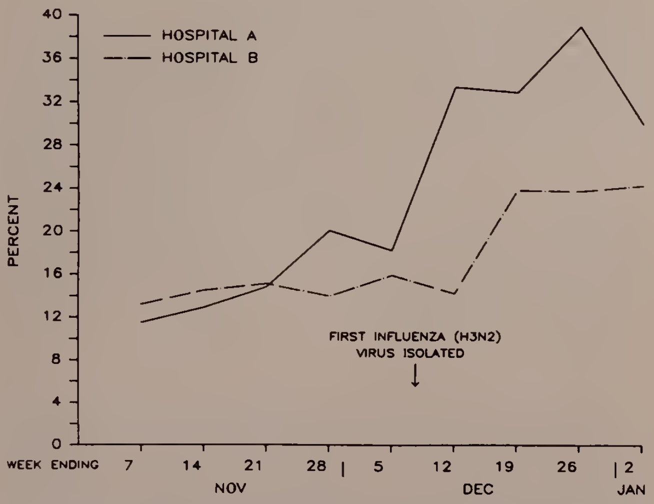

FIGURE 2. Percent of total emergency room visits for acute respiratory illness, Hospitals A and B, November 7, 1982 to January 2, 1983.

outbreaks reported in nursing homes,[3,9,10] this was a retrospective investigation. Finally, the size of the nursing home population studied totaled only 81 persons. The calculated vaccine efficacy for the chronically ill elderly population confined to institutions may, therefore, represent the minimal efficacy for influenza vaccine. Vaccine efficacy is greater for chronically ill elderly persons who are not confined to institutions.[11]

Acknowledgments. We are indebted to Dorla Johnson, Frederick Kauffman, Kathleen Rich, Meribeth Johnson, Drs Dale Morse, Peter Patriarca, Alan Kendal, and Gary Noble, the laboratory staff of the Centers for Disease Control Influenza Branch, and the staff of the United States Food and Drug Administration, Office of Biologics, Division of Virology, for assistance during this investigation, and to Jane House and Kimberly Todd for statistical assistance.

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Legionnaires' disease in a gravedigger

An epidemiologic study

ROBERT H. K. ENG, MD, MICHAEL ROTHKOPF, MD, SHARON M. SMITH, MD,
YOGESH SHAH, MD, ELENA PEREZ, MD, SARAH C. McDEARMAN, MD

ABSTRACT A gravedigger had an acute pneumonia that responded well to erythromycin therapy. His serum titer for *Legionella pneumophila* serogroup 1 rose from 1:32 during the illness to 1:532 during the convalescent period. A seroepidemiologic survey of 45 co-workers was performed, and cultures of the graveyard soil were taken.

(NY State J Med 1984; 84:238-240)

INTRODUCTION

Excavation activity has a well-known association with outbreaks of Legionnaires' disease. Examples include the epidemic of Legionnaires' disease at the Wadsworth Veterans Administration Medical Center during construction on the hospital grounds.[1] The grounds keepers had higher serum titers for *Legionella pneumophila* than did other employees who worked indoors. The immunocompromised patients at the medical center were infected by these organisms as indicated by both a rise in serotiter and isolation of the bacilli from patients. In 1965 at St. Elizabeth's Hospital in Washington, DC, an epidemic of atypical pneumonia was ascribed to Legionnaires' disease. The suspected source of the organism was an excavation site near the hospital.[2]

We recently evaluated the condition of a gravedigger with atypical pneumonia who later demonstrated a 16-fold rise in titer to *L pneumophila* serogroup 1. He was suspected to have been exposed to *L pneumophila* during work, and a seroepidemiologic survey of his family and of co-workers was performed.

CASE REPORT

A 57-year-old man was examined at the East Orange, NJ Veterans Administration Medical Center for fever, cough, and shortness of breath of two days' duration. The cough was productive of scanty amounts of thick, nonpurulent, rust-colored sputum. He denied a history of diarrhea or chills. There was no history of contact with individuals known to have active tuberculosis. He had smoked one pack of cigarettes per day for 35 years and drank approximately 1 pint of whiskey per week.

He had worked as a gravedigger for at least five years until he became ill. Excavation was performed using a grave-digging machine. The removed earth was dumped near the grave site, and in the process, an aerosol of the soil was created. Symptoms of cough and fever also developed in his 27-year-old son who lived in the same house. The son was not a gravedigger. None of the patient's co-workers had been ill recently.

On examination, the patient appeared to be well developed and acutely ill. Vital signs were as follows: rectal temperature, 39°C, heart rate, 120/min; respiratory rate, 36/min; and BP, 130/90 mm Hg. The right midchest was dull to percussion, and there were bilateral diffuse

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From the Infectious Disease Section, Medical Service (Drs Eng, Rothkopf and Shah), and the Microbiology Section, Laboratory Service (Dr Smith), Veterans Administration Medical Center, East Orange, NJ; the Department of Medicine (Dr Perez), Saint Michael's Medical Center, Newark, NJ; and the Reference Laboratory for Selected Serological Studies (Dr McDearman), Veterans Administration Medical Center, Lexington, KY.

Address correspondence to Dr Eng, Infectious Disease Consultant, Medical Service (111), VA Medical Center, East Orange, NJ 07019.

inspiratory and expiratory rales in the middle and lower posterior lung fields.

The initial chest roentgenogram showed infiltrates in the lower segments of the right upper and middle lobes. The left lung field showed some sparse, patchy infiltrates.

Gram's stain of sputum showed few polymorphonuclear leukocytes, many bronchial epithelial cells, and occasional bacteria consistent with oral flora. The routine sputum culture yielded the usual oral pharyngeal flora (mostly *Streptococcus viridans*). His hemoglobin level was 17.0 g/dL. The peripheral leukocyte count was 17,000 cells/mm^3, with a differential count of 89% polymorphonuclear leukocytes, 3% band forms, 6% lymphocytes, and 2% monocytes. The arterial blood gas obtained while he was breathing room air had a pH of 7.57, P_{CO_2} of 27 mm Hg, and P_{O_2} of 45 mm Hg.

Initial treatment consisted of antibiotics directed toward the possibility of aspiration pneumonia (clindamycin and tobramycin).

After receiving these antibiotics for two days, the peripheral leukocyte count rose to 21,000 cells/mm^3 with 24% band forms. His rectal temperature rose to 40°C with no diurnal variation. Erythromycin therapy was initiated, and the patient had an uneventful recovery and was discharged from the hospital after four weeks. Two days after hospital admission, the serum indirect fluorescent antibody titer to *L pneumophila* serogroup 1 was 1:32 and two weeks later was 1:512. A diagnosis of legionellosis was then confirmed based on these results.

METHODS AND RESULTS

Three months after the patient's illness, serum samples were obtained from all members of his household and all working members of the local gravediggers' union. Serum samples from five family members and from 45 gravediggers were tested for the presence of *L pneumophila* antibodies by indirect immunofluorescent antibody technique (Reference Laboratory for Selected Serological Studies, Veterans Administration Medical Center, Lexington, KY). Samples were tested for antibodies to *L pneumophila* types 1 to 6. Titers of 1:128 or higher were interpreted as recent or past infection. The patient's son, who had symptoms of upper respiratory tract infection, had a titer of 1:1024 to serogroup 1. Five gravediggers (11.1%) had titers of 1:128, and 21 (46.6%) had titers of 1:64 (Fig 1). The gravediggers most frequently showed a reaction to serogroups 5 or 6, though in low titers. Soil from the graveyard in question was also examined for presence of Legionella organisms. Random samples of the surface soil were sent to the Laboratory Service of Veterans Administration Medical Center, Buffalo, NY for stain and culture. Samples from both sites showed many organisms with the direct fluorescent staining technique, but only one of two sites showed Legionella organisms, identified as *L micdadei*.

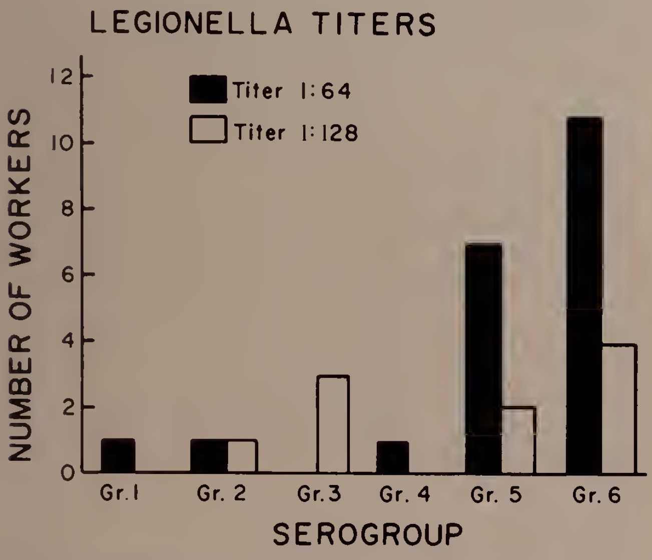

FIGURE 1. Distribution of gravediggers with reactive serum samples to *Legionella pneumophila* serogroups 1 to 6.

DISCUSSION

A patient with Legionnaires' disease was initially suspected of having acquired the organism during excavation, and this hypothesis led to an examination of his co-workers for evidence of recent or past infections with Legionnaires' disease bacilli. Gravediggers and other excavators are exposed to aerosols of earth that may contain soil commensals such as Legionnella organisms. They may be expected to have substantial titers to these organisms should past exposure have resulted in clinical or subclinical infections. Yet, in a survey of 45 co-workers, only five had titers of 1:128, and interviews with co-workers failed to reveal any cases of pneumonia deaths or illnesses attributable to Legionella organisms in the past. The prevalence of five of 45 (11.1%) co-workers with substantial titers is similar to that of selected populations in New York City with positive serologic findings (12% to 15%).[3] The patient's son had no exposure to excavation sites, yet he was ill during the same month in which pneumonia developed in his father. Some area within the home would probably be implicated as the source for the Legionella organisms. Because all other members of the patient's household did not have significant antibody titers ($\geq$1:128) to *L pneumophila* serogroups 1 through 6 and were not recently ill, the source of the organism infecting our patient cannot confidently be attributed to the patient's residence. Unfortunately, the water system of the residence was not sampled for Legionella organisms, but presumably all family members would have been affected if the water contained the organisms. Cultures of the graveyard soil revealed *L micdadei*, an organism different from the one that presumably infected our patient. Thus, the source of the organism remains unknown.

Most previous epidemics of Legionnaires' disease have been traced to aerosolized *L pneumophila* from air conditioners,[4] showers, or excavations of earth.[1,2] Nevertheless, such epidemics are rare, and most people exposed to air conditioners, showers, and excavation sites do not manifest symptoms or seroconvert with antibodies to Legionnaires' bacilli. Routine environmental cultures have not been considered helpful in predicting outbreaks because of the ubiquitous nature of the organism in water and soil.[5] Cordes et al[6] were able to culture organisms from water after thorough sterilization of the water system.

The factors determining which excavation sites are hazardous remain unknown. Considerations may include the amount of moisture in the soil, the depth of the excavation, the amount of aerosol created, the bacterial density in the soil, the ambient temperature, humidity, time of year, and the virulence of the local Legionella strains. Other factors determining whether clinical or subclinical disease will occur are related to the nature of the host's immune defenses. During the excavation and the outbreak at St Elizabeth's Hospital, the patients acquired the disease while the excavators remained healthy; the few excavators whose serum samples were tested had substantial antibody titers.[2]

Our seroepidemiologic study does not show that the excavators are at increased risk for Legionnaires' disease. In this regard, our results are similar to the findings of Goldman and Marr,[7] who evaluated risk to air-conditioning maintenance workers of legionellosis. Although we demonstrated that Legionella organisms are not difficult to find in soil, the gravediggers failed to show increased risk for subclinical infections as demonstrated by a lack of seroconversion. Unless an outbreak of clinical disease of legionellosis is demonstrated among excavators, performing extensive serologic studies and environmental cultures in sporadic cases in this population group is both unproductive and unwarranted.

Acknowledgments. Leon G. Smith, MD, Chief of Medicine, Saint Michael's Medical Center, organized the epidemiologic survey of the gravediggers, and Thomas Beam Jr, MD, Chief of Infectious Diseases Section, Buffalo Veterans Administration Medical Center, coordinated the soil sample cultures.

This study was supported in part by the General Medical Research Funds of the East Orange, NJ Veterans Administration Medical Center.

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REVIEW ARTICLE

Viral infections in immunosuppressed patients

SHALOM Z. HIRSCHMAN, MD

HOST DEFENSE MECHANISMS AGAINST VIRAL INFECTION

Viral infection is an important complication of iatrogenic immunosuppression, whether in the patient receiving immunosuppressant chemotherapeutic drugs for therapy of neoplasia, especially hematopoietic neoplasia, or in the patient receiving immunosuppressive therapy following organ transplantation.

To appreciate the susceptibility of the immunosuppressed patient to viral infection, a review of the general mechanisms of host defenses against viruses is required.[1] Viral infections in animals induce humoral antibodies to both the complete infectious particle—usually to surface components of the virion—and to internal components of the infecting virus.[2] These antibodies neutralize the virus, thus decreasing its infective ability. Antibodies in serum and extracellular fluid constitute the main protective arm against primary viral infections by neutralizing the virus at the site of entry into the host. The degree of protection against viral infection is directly correlated to the level of neutralizing antibody in the blood when viremia is an essential pathway in the pathogenesis of the viral infection, such as is found in infections with measles, poliomyelitis, yellow fever, and smallpox. Immunoglobulin (Ig)A antibodies are important in the protection against infection of body surfaces such as the respiratory and gastrointestinal tracts. Thus, IgA antibody has been shown to protect against infection with influenza virus.

Although antibodies are important in protecting the host against primary viral infection, they are much less important in recovery from an established viral infection.[3] Here cell-mediated immunity appears to be the dominant defense mechanism. Thus, patients born with congenital agammaglobulinemia, but who develop cell-mediated immunity, usually recover from viral diseases without difficulty. However, patients with defective cell-mediated immunity may have severe viral infections such as vaccinia gangrenosa following vaccinia inoculation. Antilymphocyte serum, which decreases the T-cell population in animals, increases the severity or duration of infection with viruses,[4] especially those that possess envelopes such as the herpes viruses, pox viruses, and paramyxoviruses. Cell-mediated immunity also is important in maintaining the suppression of latent viral infections such as those induced by the herpes simplex virus (HSV), herpes zoster virus (HZV), cytomegalovirus (CMV), measles virus, human wart virus, and the human polyoma viruses (papova viruses).

In addition to the immunologic mechanisms of host defenses against viral infection there are nonspecific factors that affect the resistance of the host: interferon, the nutritional state of the host, hormones, temperature, and nonspecific inhibitors of viral infections such as globulins and lipoproteins found in sera of animals that can neutralize the infectivity of many enveloped viruses. Interferon, a substance released by cells after viral entry, inhibits viral multiplication by preventing the synthesis of viral proteins.

Malnutrition influences many aspects of host defenses and increases the severity of viral infections, as illustrated by the devastating effects of measles in malnourished children. Several infections, such as polio and coxsackievirus myopericarditis, may be increased in severity in pregnancy. Adrenal corticosteroids enhance the susceptibility of animals to neurotropic viruses and to coxsackieviruses.[5] High body temperature may help reduce the severity of viral infection in the host.

The cellular responses of the host to viral infection can be divided into specific and nonspecific types. The specific response is the generation of virus-specific cytotoxic T-cells, which act on host cells that contain virus and express viral antigens or altered cellular antigens. The nonspecific cellular responses include the activation of macrophages and natural killer (NK) cells. The cytotoxic T-cells are specific for HL (histocompatibility locus) A antigens,[6] but the NK cell once activated has broad cytotoxic effects.[7] One of the proposed mechanisms for NK cell-mediated lysis involves the activation of NK cells by interferon produced in virus-infected cells. This mechanism accounts for the protection of uninfected target cells. Thus, NK cells would selectively eliminate virus-infected cells and play a major role in nonspecific resistance to virus infections. It is interesting to note that patients with X-linked lymphoproliferative syndrome, who have a genetic deficiency that renders them susceptible to Epstein-Barr virus (EBV) infection, often resulting in lymphoma, have been shown to have reduced

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Address correspondence to Dr Hirschman, Director, Division of Infectious Diseases, The Mount Sinai Medical Center, One Gustave L. Levy Place, New York, NY 10029.

levels of NK-cell activity in their blood.[8]

MAJOR VIRAL INFECTIONS IN IMMUNOSUPPRESSED PATIENTS

The major viral infections observed in immunosuppressed patients are caused by members of the herpes virus group, such as CMV, HZV, HSV, EBV, and the human polyoma viruses (papova viruses) such as the JC and BK viruses related to simian virus 40 (SV40). It is interesting that these viruses all contain a DNA genome and can become latent. Furthermore, these viruses have been implicated in human carcinogenesis and can cause cellular transformation in many cell-culture systems. Epidemiologic studies also support the conclusion that many of the viral infections observed in immunosuppressed patients are due to the activation of latent viruses previously acquired.[9] Hepatitis B virus (HBV) infection, including reactivation of previously acquired infection, has also been observed in immunosuppressed patients; HBV contains a DNA genome and has been implicated in the cause of primary hepatocellular carcinoma.[10]

Patients receiving organ transplants are susceptible to viral infections, especially the reactivation of latent viruses. These patients often receive multiple blood transfusions and are at risk of infection with CMV, EBV, HBV, and non-A, non-B hepatitis virus.

Cytomegalovirus infections. CMV appears to be the most important agent complicating transplantation. Fiala et al[11] reported active CMV infection in 96 percent of patients after renal transplantation. Reactivation of HSV, varicella zoster virus (VZV), and EBV was found in 35%, 24%, and 0% of patients, respectively. Viremia with CMV developed in 42% of patients an average of two months after renal transplantation and lasted 1.75 (±1.5) months. Viremia was followed by chronic viruria. Clinical syndromes caused by CMV infection include fever, arthralgia, pneumonitis, and leukopenia. Rejection of renal transplants is also more common in patients with proved CMV infection, although the incidence of rejection is higher with primary infection. Naraqui et al[12] found an incidence of infection with CMV of 73%; HSV, 57%; EBV, 30%; and VZV, 7% in renal allograft recipients. Myocarditis and encephalitis have also been reported in patients with CMV infection; hepatitis in these patients is usually mild. It is unclear whether infection with CMV acts as an adjuvant and triggers rejection of the renal allograft or whether rejection activates the latent virus infection.[13]

Epstein-Barr virus infections. The manifestations of EBV infection depend on the immunocompetence of the host.[8] The immune response to infection with EBV is complex. B cells possess receptors for EBV and are transformed by the virus; indeed, infected B cells can be immortalized in cell culture. Infection with EBV appears to activate NK cells and T-suppressor cells. EBV-specific antibodies against viral capsid antigen (VCA) of IgM and later IgG types are produced. Anti-early antigen (EA) antibodies appear transiently and are followed by anti-EB nuclear associated antigen (EBNA); the latter antibody response requires T-cell killing of infected B cells. Late-appearing memory T-cells and IgG anti-VCA antibodies may persist for life. EBV may also remain latent for life in the individual's B cells. Immunosuppression may reactivate the virus with reappearance of anti-EA. Indeed, about 1 in 100 renal transplant recipients develop fatal EBV-induced B-cell proliferation.

Patients with inherited immunodeficiency disorders also are at increased risk of developing EBV-induced diseases. Males with X-linked lymphoproliferative syndrome (XLP) develop four types of clinical courses after infection with EBV: chronic or fatal infectious mononucleosis, aplastic anemia, agammaglobulinemia or hypoglobulinemia, or malignant lymphoma.[8] Immunosuppressed renal transplant recipients also may develop an infectious mononucleosis-type disease or malignant lymphoma. Diffuse polyclonal B-cell proliferation may complicate renal transplants in young patients that acquire primary EBV infection; these patients show a low or absent anti-VCA and anti-EA with no, or very low, anti-EBNA. Older patients with reactivation of EBV due to immunosuppression show elevated anti-VCA, anti-EA, and anti-EBNA and develop polyclonal or monoclonal malignant lymphomas.

Varicella-zoster virus infections. VZV infections are common in immunosuppressed patients. Such patients may develop disseminated HZV infection complicated by pneumonia and encephalitis.[14] It is not clear what factors control HZV infection; IgM antibodies are found in varicella and also in zoster. VZV antibodies appear more rapidly and in higher titers during episodes of zoster than during chickenpox, a situation that is compatible with the anamnestic response following reactivation. Renal transplant patients monitored for several years show fluctuations in VZV complement-fixing antibody titers suggesting that subclinical virus release and antigenic stimulation may be involved in maintaining prolonged immunity.[9] In addition, antibody may have a protective role in prophylaxis of high-risk groups against varicella when given soon after exposure.[15] Such VZV immunoglobulin is ineffective late in the incubation period or when the disease has become apparent. Lymphocyte transformation by viral antigens appears to be an indicator of past exposure to VZV. A variety of cell types are involved in the response to VZV replication, including T-lymphocytes and NK cells. VZV remains in latent form in the sensory ganglia and when activated travels down the axon to proliferate in the skin. Patients with leukemia, lymphoma, or Hodgkin's disease are more likely to develop severe progressive disseminated VZV infection. Visceral dissemination with varicella occurs in 20% to 35% of children receiving chemotherapy for cancer, with a mortality of 7% to 30% from varicella pneumonitis and encephalitis; these children have low or absent circulating VZV antibodies. The risk of developing zoster in patients with Hodgkin's disease is 13% to 15%; in patients with non-Hodgkin's lymphoma, 7%; and 1% to 3% in patients with solid tumors. About 15% to 30% of patients with Hodgkin's disease and zoster show dissemination.

Herpes simplex virus infections. HSV infection is also more common in patients with immunosuppression.[9] These infections can be localized in the oral pharynx or to an area of the skin, or they can be disseminated, with complicating esophagitis, pneumonitis, and encephalitis.

Human polyoma viruses. The polyoma-like human viruses, the JC and BK viruses, are also found in patients with immunosuppression.[16] Viruria with the BK virus is often found in renal transplant patients. There is still a question as to whether or not this viruria is associated with increased risk of rejection. The virus does proliferate in the urothelium[17] and can cause ureteral obstruction due to a proliferation of the urothelial cells. The JC virus has been associated with multifocal leukoencephalopathy in patients with severe immunosuppression.[18]

Hepatitis viruses. Infections with hepatitis viruses are also common in immunosuppressed patients.[10] Screening of blood donors has diminished the incidence of infection with HBV. The role of non-A, non-B viruses in immunosuppressed patients, especially with transplanted organs, is not clear. Immunosuppression increases the replication of HBV both in humans and animals and leads to a chronic aggressive hepatitis. On the other hand, patients with active hepatitis do not have a serious problem with rejection of renal transplants. Indeed, renal-allograft recipients who are HBV carriers, especially those without antibody to hepatitis B surface antigen (HB_sAg), and recipients with non-A, non-B hepatitis have been shown to have a low probability of graft rejection.[19]

ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

Although this review has emphasized viral infections complicating immunosuppression, the discussion would be incomplete without a consideration of the recently described Acquired Immunodeficiency Syndrome (AIDS).

In 1979–1980 there was a cluster of five cases of *Pneumocystis carinii* pneumonia in previously healthy young men in Los Angeles. *P carinii* is a protozoan parasite that was first recognized in Europe in the 1940s as a cause of plasma cell pneumonia in malnourished infants. The organism was later found in the United States in immunocompromised patients with pneumonia. Most of these patients had underlying acute leukemia or lymphoma and were often treated with corticosteroids. Therefore, the infection in previously healthy young males was quite surprising. Soon it became evident that both *P carinii* pneumonia and Kaposi's sarcoma were appearing in homosexual young men in New York City and Los Angeles. It was quickly appreciated that these patients were suffering from a profound disturbance of cellular immune function first called Gay Related Immunodeficiency (GRID) Syndrome, and then Acquired Immunodeficiency Syndrome (AIDS), when it was realized that heterosexual patients abusing drugs were also at risk. The disease was also recognized in Haitian immigrants and in a few patients with hemophilia. Between June 1, 1981 and December 31, 1983, 3,000 cases were reported from 42 states and 16 countries to the Center for Disease Control (CDC). The groups at risk for AIDS now are known to include homosexual and bisexual men, intravenous drug abusers, Haitians living in the United States and Haiti, individuals with hemophilia receiving factor VIII concentrate, female and male sexual partners of patients with AIDS, and infants and children of high risk populations.[20]

In addition to predilections to infection with *P carinii* and to developing Kaposi's sarcoma, these patients are prone to infections by organisms that are warded off by the cell-mediated immune mechanisms of the host. These organisms include fungi such as *Candida albicans*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Petriolydiumboydii* and *Aspergillus* spp; protozoa such as *Toxoplasma gondii*, causing encephalitis in these patients, *Cryptosporidium* spp and *Isospora belli*, causing enteritis; *Mycobacterium avium-intracellulari* and *Mycobacterium tuberculosis*; other organisms such as *Nocardia* spp and *Legionella* spp; and viruses, including Epstein-Barr virus (EBV), causing lymphoma; cytomegalovirus (CMV), causing either disseminated disease, pneumonia, retinitis or encephalitis; herpes simplex virus (HSV); herpes zoster virus (HZV); and progressive multifocal leukoencephalopathy. Infections in these patients are quite difficult to treat.[20]

In addition to Kaposi's sarcoma, other neoplasms, including non-Hodgkin's lymphoma and rectal carcinoma, have been recognized in these patients. A curious thrombocytopenic purpura also has been described in this group of patients.[21] Another enigmatic syndrome found in groups at risk for AIDS is a prolonged, unexplained lymphadenopathy, with or without fevers and night sweats, termed lymphadenopathy-fever syndrome.[22]

The immunodeficiency in these patients affects mainly the T-lymphocyte population.[20] B-cell numbers are normal, while IgA and IgG concentrations are increased, as are levels of circulating immune complexes in patients with opportunistic infections. Although infection with common bacterial pathogens is infrequent, antibody responses to primary immunization may be somewhat reduced. Lymphopenia (less than $1500/mm^3$) is often present in patients with AIDS and opportunistic infection but in only 50% of patients with Kaposi's sarcoma. There are reduced numbers of T-helper cells, with reduced helper to suppressor ratios. The functional capacity of T-cells is reduced, as manifested by skin test anergy and in vitro assays for proliferative responses to mitogens or antigens.

The prognosis of patients with opportunistic infections is extremely poor with a median survival time of approximately six months. Most patients are deceased within two years of diagnosis. Death is usually caused by a disseminated opportunistic infection.

Although the specific etiologic agent of AIDS is not yet known, the epidemiology of the disease does point to an infectious agent. Furthermore, the frequency of unusual neoplasms such as Kaposi's sarcoma in patients with AIDS offers the opportunity to study the mechanisms of human carcinogenesis.

Several viruses have received attention as possible causes of AIDS. There is a very high incidence of cytomegalovirus, Epstein-Barr virus and hepatitis B virus infections among the populations at risk of developing AIDS.[20] The Epstein-Barr virus has been implicated as the etiologic agent of Burkitt's lymphoma and other types of lymphoma. During the past decade, there has been interest in cytomegalovirus as a possible cause of Kaposi's sarcoma. Indeed, a study of the DNA from Kaposi's sarcoma tissue by DNA/DNA reassociation kinetics indicated that human CMV DNA sequences were sometimes found in tumor DNA.[23] Human CMV does have a broad range of cell tropism including lymphocytes, granulocytes, epithelial cells and fibroblasts. Murine cytomegalovirus has been an experimental tool for inducing dysfunction of cell-mediated immunity in animals. However, both CMV and EBV are so common in the AIDS-affected populations that the possible role of these viruses as etiologic agents will require careful and extensive studies. Infection with hepatitis B virus is also found in populations at risk for AIDS. Chronic infection with this virus has been associated with subsequent development of primary hepatocellular carcinoma in areas of the world where this infection is endemic. Recently, Siddiqui[24] reported the presence of hepatitis B virus-related sequences in DNA prepared from two patients with Kaposi's sarcoma. One of these patients had no other markers for hepatitis B virus infection.

A virus that has recently generated much interest as a possible cause of AIDS is the human T-cell leukemia virus (HTLV). HTLV is a retrovirus associated with adult T-cell leukemia in Japan and more sporadically in the United States. Endemic areas of HTLV infection have been found in the Carribean[25] as well as in Japan.[26] A recent serologic survey showed that approximately 25% of patients with AIDS have antibodies to HTLV.[27] In addition, the virus has been isolated from the lymphoid tissue of two patients with AIDS.[28-30] However, it is still not known whether this virus is an etiologic agent or just a secondary invader. HTLV was first isolated from peripheral blood lymphocytes from a black patient with an aggressive cutaneous T-cell lymphoma. Another related virus was isolated from another black patient with a disorder resembling Sezary's syndrome. Adult T-cell leukemia-lymphoma, as described in blacks from the West Indies, is characterized by an aggressive clinical course with lymphadenopathy, hypercalcemia and a leukemic blood picture with lymphocytes of a mature (OKT4+, TdT−) membrane phenotype. Two main geographic sites of the infection have been found in the Carribean and in Southern Japan, but sporadic cases have appeared in many parts of the world. There is a high prevalence of antibodies to HTLV, not only in patients, but also in patients' relatives and in healthy persons in endemic areas. There is evidence for horizontal spread of the virus. Whether HTLV is a cause of AIDS will require, at the very least, careful studies of the virus in the various stages of the disease in large populations of the high risk groups.

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Vesicular rash and bilateral pulmonary infiltrates in a 67-year-old woman with Hodgkin's disease

CASE PRESENTATION

G. Robert Thompson, MD (Third Year Resident in Medicine): A 67-year-old woman under treatment for recurrent Hodgkin's disease was transferred from another hospital with disseminated mucocutaneous herpes zoster and bilateral pulmonary infiltrates. Hodgkin's disease was first diagnosed three and a half years earlier upon biopsy of a right cervical node. Laparotomy and splenectomy indicated stage III-A disease. Following radiation therapy, she did well during the subsequent three years. Six months prior to the present admission, she was treated with local irradiation for recurrent adenopathy in the right cervical area. She did well for five months, but a follow-up chest film revealed "early pneumonia." Tetracycline was given for suspected mycoplasma pneumonia.

Shortly thereafter, a vesicular rash developed over the right breast area. A diagnosis of herpes zoster was made, and the patient was treated with intramuscular steroids and gamma globulin. Within several days, the rash spread requiring her admission for intravenous acyclovir treatment. The rash and the pulmonary infiltrates persisted. On the third hospital day, the patient became febrile and dyspneic, with a fall in serum bicarbonate level. She was transferred to this hospital for additional treatment.

On admission the patient was acutely ill and dyspneic with a respiratory rate of 40 to 45/min. Her blood pressure was 120/70 mm Hg; the heart rate was 110/min and regular. An extensive weeping vesicular rash covered her entire body, including all visible mucous membranes. No adenopathy or nuchal rigidity was present. Breath sounds were normal and well transmitted bilaterally with a few crackling rales at the bases. Cardiac examination revealed only the tachycardia; the remainder of the physical examination was noncontributory.

Laboratory examinations included a serum sodium of 125 mmol/L, CO_2 content of 10 mmol/L, and an initial anion gap of 16 mmol/L; blood urea nitrogen (BUN) 42 mg/dL, creatinine 1.7 mg/dL; arterial pH 7.41, Pco_2 17.0 mm Hg, Po_2 50 mm Hg. Her initial lactic dehydrogenase (LDH) was 1,176 U/L (normal 60 to 225 U/L); the serum glutamic oxalacetic transaminase (SGOT) was 1,090 U/L (normal 0 to 40 U/L) and the alkaline phosphatase was 145 U/L (normal 30 to 100 U/L). The serum lactate level was 10.3 mmol/L (normal 0.5 to 2.2 mmol/L). The urine sodium was less than 10 mmol/L. The initial chest film showed diffuse bilateral interstitial infiltrates and normal cardiac size and shape.

The initial impression was disseminated herpes zoster with zoster pneumonia, severe lactic acidosis, respiratory alkalosis, hypoxemia, hepatocellular necrosis, and recurrent Hodgkin's disease.

Therapy was initiated with Ara-A(adenosine arabinoside) 10 mg/kg/day. Continued dyspnea, deterioration of blood gas levels, and progressive lactic acidosis necessitated endotracheal intubation and intravenous alkali and fluid therapy. A total of 650 mEq of sodium bicarbonate was administered, despite which the serum lactate level rose from 10.3 to 18.3 mmol/L, and the blood pH fell to a low of 7.15. Worsening hypoxemia and progressive hypotension indicated the need for monitoring with the aid of a Swan-Ganz catheter and inotropic support. In the face of unrelenting acidosis and cessation of urine output, further aggressive support was unavailing, and the patient died on the third hospital day.

H. Rodney Hartmann, MD (Radiologist-in-Chief): The initial chest film obtained on the day of admission revealed a diffuse infiltrate throughout both lung fields, interstitial in character, most marked in the right lower lung field and in the posterior basal segment of the lower lobe of the left lung. The right hilar shadow was prominent. The cardiac silhouette was normal.

With no prior films for comparison, we assumed that these infiltrates were acute and related to the present illness. The type of infiltrate is certainly compatible with that attributed to varicella pneumonia. Some descriptions of that condition refer to a homogeneous miliary type of infiltrate; but most such patients present a patchy appearance that over several days regresses in some areas and progresses in others.[1] In this patient, the infiltrate was not specific in pattern or distribution and was compatible with any bacterial or viral pneumonia, as well as other lung conditions.

Late on the first hospital day, a repeat chest roentgenogram indicated the presence of an endotracheal tube, with

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Based on the clinicopathologic conference (CPC) held at Mary Imogene Bassett Hospital, Cooperstown, New York, May 12, 1983.

Moderator: Harlan D. Alpern, MD, Pathologist-in-Chief.

Clinical Discussion: Richard J. Horner, MD and Richard E. Reese, MD, Attending Physicians. *Pathology Presentation:* Dr Alpern.

Editor: JOHN T. FLYNN, MD.

Address correspondence to Dr Flynn, Consulting Editor, *New York State Journal of Medicine*, PO Box 5404, 420 Lakeville Rd, Lake Success, NY 11042.

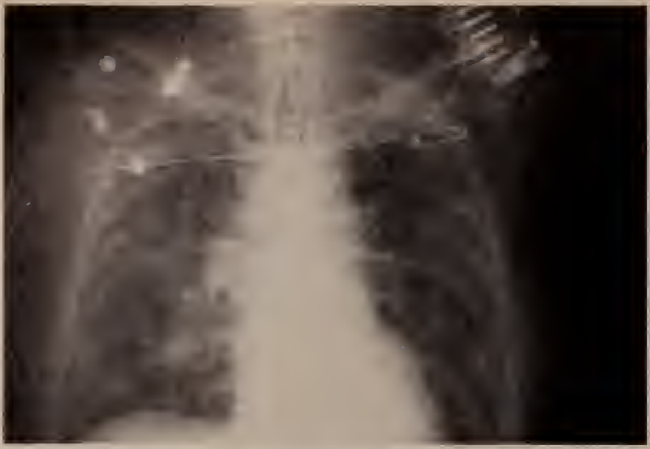

FIGURE 1. Final chest x-ray on second hospital day showing extensive diffuse bilateral pulmonary infiltrates.

FIGURE 2. Watercolor by Carswell, showing lymph node involvement in patient in Hodgkin's original series.[14]

the tip in the right main-stem bronchus; no atelectasis was evident. The infiltrate appeared unchanged. A follow-up roentgenogram obtained shortly thereafter showed the endotracheal tube properly placed, with no change in infiltrate; the cardiac silhouette remained normal.

The final film of the chest, taken late on the afternoon of the second hospital day (Fig 1), again revealed the presence of the endotracheal tube and of a Swan-Ganz catheter, both in proper place. The lung fields showed a marked increase in infiltrate, now diffuse, perhaps granular in nature; the normal cardiac size and silhouette made congestive failure unlikely. Diffuse aspiration pneumonia was another possibility, but the acute onset of the adult respiratory distress syndrome (ARDS), superimposed on the pulmonary process evident on admission, would be more likely.

Since varicella pneumonia was a consideration, I would like to add that patients hospitalized with that condition represent a select group having a relatively poor prognosis. Studies of such patients indicate that approximatey 10% die; the mortality in pregnant women exceeds 40%. In those who recover there may be residual scarring in the lung, and in a small percentage of such patients there is a distinct pattern of microcalcification that persists indefinitely. Obviously, only a small number of patients with varicella pneumonia are hospitalized, and the morbidity and mortality for all cases are significantly lower than the figures I have just quoted.

Dr Thompson: Initially this patient presented with a compensated metabolic acidosis as indicated by a normal pH and a very low bicarbonate level, but she rapidly progressed into a decompensated state with an increase in P_{CO_2}, decrease in blood pH, and no change in bicarbonate level. Further decompensation led to a very low pH, a fall in bicarbonate levels, a rise in P_{CO_2}, and eventually complete resistance to intravenous bicarbonate therapy; the anion gap continued to increase as production of lactic acid continued. In a series of 30 consecutive patients in shock, studied by Blair,[2] the average lactate level on admission of 18 survivors was 2.8 mmol/L, with few above 3.5 mmol/L. Of the 12 patients who died, however, the average lactate level was 6.2 mmol/L; in only two was it below 4.2 mmol/L. Thus, the initial lactic acid levels were generally predictive of the outcome. The initial lactic acid level in our patient was 10.3 mmol/L, well above those reported in Blair's study. One other predictive correlate in this study was marked hypocapnia with a low or normal blood pH, as evident in our patient.[2] Poor correlation was found by Blair between outcome and such correlates as blood pressure, initial blood pH, or cardiac output.

Richard J. Horner, MD (Attending Physician): In 1832 Dr Thomas Hodgkin described seven patients with massive enlargement of the "absorbent glands" (lymph nodes), mainly above the clavicles and in the axillas (Fig 2). A half-century passed before the definitive morphologic features of this disease were identified. Reexamination of Dr Hodgkin's original pathologic material, nearly 100 years after his initial description, confirmed the correctness of his diagnosis in four of his original cases. In subsequent large series, evidence of involvement of supraclavicular or mediastinal nodes, or both, and frequently of axillary nodes was present in two thirds of the cases; Waldeyer's ring area and the epitrochlear nodes are rarely affected, in contrast to their involvement in non-Hodgkin lymphoma.

Until about 20 years ago, the prognosis in the patient with untreated disease, including all stages, was five-year survival in fewer than 10% of patients; by 10 years nearly all patients were dead. By the 1950s development of orthovoltage radiation treatment permitted a 25% long-term survival. The next two decades saw the advent of megavoltage radiation, which effected a five-year survival rate of nearly 80% and a 10-year survival of 62% for patients with all stages of the disease, with or without additional chemotherapy[3] (Fig 3).

In the modern era, the process of staging the disease has identified two groups of patients with quite different prognoses—localized disease confined to one or two lymph node regions on the same side of the diaphragm, with long-term survival exceeding 80%, in contrast to disease on both sides of the diaphragm or involving parenchymal organs, or both, associated with cure rates of about 50%.[3]

A third great advance was the development of combination chemotherapy in the mid-1960s, capable of producing long-term disease-free survival in at least half the

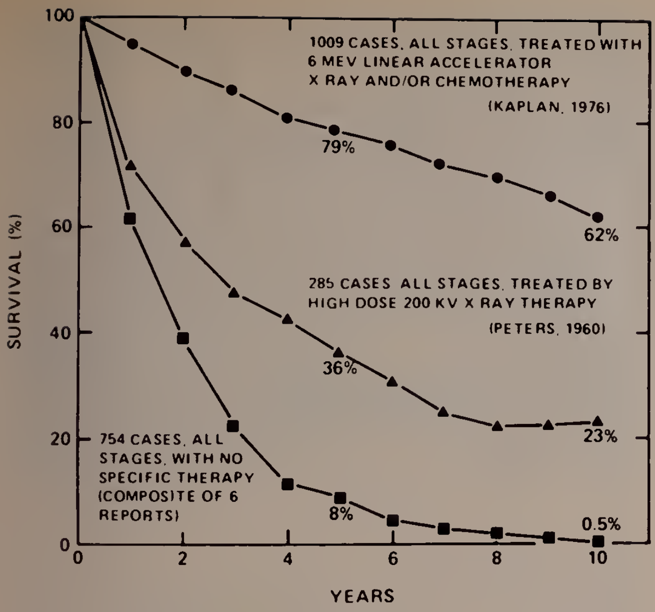

FIGURE 3. Results of radiation therapy on patients with Hodgkin's disease.[3]

patients, and complete remission in 80% of previously untreated patients with stage III or IV disease. A 10-year follow-up of the first 200 patients treated with MOPP (nitrogen mustard, Oncovin-vincristine, procarbazine, prednisone) therapy showed the overall survival to be 60%; and in those in whom complete remission had been achieved the disease-free survival was over 60%. No relapses were seen after remissions of three and a half years' duration.[4] An unresolved question is the optimal approach to the patient with parenchymal organ involvement and constitutional symptoms.[5]

The patient we presented experienced relapse after radiation therapy. In general, relapse even involving a single node or nodal region is tantamount to dissemination, so that combination chemotherapy is indicated. MOPP therapy is well-established as the salvage treatment for radiation-therapy failures, since remissions are achieved in about three quarters of such patients, most of which are long-lasting.

Ever since the earliest microscopic descriptions, there has been uncertainty as to whether the presence of giant cells, inflammatory cells, and fibrosis represents an infection or a true neoplasm. The Reed-Sternberg giant cells can proliferate in culture and are transplantable, suggesting the possibility of neoplastic origin, although the neoplasm may be a reaction to infection.[6]

Subsequent to Dr Dorothy Reed's identification of tuberculin anergy in patients with Hodgkin's disease at the turn of the century, varying degrees of nonreactivity to natural and synthetic antigens and diminished responsiveness to various lymphocyte stimulants have been found to be typical of most, if not all, patients with this disease. This immunologic impairment is to a degree proportional to the extent of the disease and can linger long after the completion of successful combined modality therapy.[6]

Richard E. Reese, MD (Attending Physician): Varicella zoster virus is a member of the herpes virus group, which includes herpes simplex, Epstein-Barr virus, and cytomegalovirus. They contain DNA, which is important since DNA inhibitors, such as adenine arabinoside (Ara-A, vidarabine), are used in antiviral therapy. The initial infection with varicella virus causes chickenpox; recovery is followed by latent infection, persisting for decades, presumably in the dorsal root ganglia, and becoming reactivated with advancing age or with decrease or loss of cell-mediated immunity. Zoster usually presents with a vesicular eruption, with one to three dermatomes involved.[7] Dissemination occurs in a small percentage of otherwise healthy people and in larger numbers of immunocompromised subjects, either to the skin, or to the skin together with lungs, central nervous system, liver, or pancreas, or some combination of these. In about 20% of immunocompromised patients in whom segmental zoster develops, complications will also develop, often preceded by cutaneous dissemination and sometimes only by uveitis or central nervous system involvement.[8] Interestingly, the initial infection may occur in utero, and neonatal zoster may develop at three or four months of age.

Disseminated zoster first presents with a local segmental lesion and then may spread within a few days either to the skin or to skin plus viscera. In the present case, the patient's lungs appeared to be involved; the patient likewise presented symptoms compatible with meningoencephalitis, although we do not have any results of a lumbar puncture. Such a procedure probably would not have affected either her therapy or clinical course. The overall mortality in disseminated varicella zoster is not high (usually under 3 to 5%), but the risk is clearly increased when the lungs are involved with viral pneumonia.[7,8] In patients with underlying reticuloendothelial cancers, rates of clearing the virus are slower and the incidence of dissemination is higher. Antibody to the virus is often present but seems not to be important to the individual patient's immunity. Depression of the patient's cell-mediated immunity is important in the pathogenesis of disseminated disease.

Until recently there has been no readily available treatment for complicated or potentially complicated herpes zoster infections. A multicenter study in the mid-1970s suggested that adenine arabinoside (Ara-A) had promise as a therapeutic agent. A recent, multicenter, double-blind, randomized, placebo-controlled study of 120 immunosuppressed patients, with segmental herpes zoster, demonstrated that vidarabine was valuable in reducing the complications of herpes.[8] These patients had been or were being treated with antineoplastic chemotherapy. The treated patients in this study were given, within 72 hours of the onset of disease, Ara-A, 10 mg/kg/day intravenously over 12 hours for five days. Cutaneous dissemination was defined as more than 100 vesicles distal to the involved dermatome; visceral dissemination was suggested by uveitis, meningoencephalitis with confirmatory spinal fluid pleocytosis and negative bacterial and fungal cultures, pneumonitis with bilateral interstitial infiltrates and supportive clinical findings, hepatitis with abnormal hepatocellular function tests, or any combination of these. A lung biopsy was not required to exclude other opportunistic lung infections. The results of this study indicated that the group treated with Ara-A had a much lower incidence as well as decreased severity of cutaneous and visceral dissemination; the frequency of postherpetic neuralgia was not diminished, although severity and duration were lessened. The surface area of segmental zoster lesions present in the control group continued to increase in size, whereas such lesions in the treated group did not. The therapy appeared to be well tolerated. The risk factors for dissemination included increased age and underlying lymphoproliferative disease. Underlying lymphoproliferative disease with cutaneous dissemination, at the time of admission, as in our patient, was predictive of visceral involvement. Again, mortality was higher in patients with dissemination and pneumonitis.

This study was not designed to determine the effectiveness of Ara-A in the treatment of disseminated disease with visceral involvement. In treating our patient, who appeared to have signs of visceral involvement, however, we believed we had no choice but to initiate Ara-A treatment in the hope of affecting her clinical course, even though irreversible tissue damage may have already occurred by the time of her admission.

Acyclovir has been used to treat herpes zoster,[9] although the experience with its use in the therapy of herpes simplex is more extensive. To my knowledge, there are no published controlled studies in which acyclovir therapy is compared with Ara-A therapy for herpes zoster, but these studies are underway. There appears to be more clinical experience with the use of Ara-A in herpes zoster infections. Interferon has been used for segmental zoster in patients with cancer, but it is not always available. Zoster immune globulin may be useful in immunosuppressed children exposed to varicella, but it is not indicated in the prevention or treatment of zoster, since zoster can develop even in the presence of antibody.[7] A live attenuated varicella vaccine presently under development in Japan is intended to prevent varicella infections in children, but it has no role in the prevention or treatment of zoster.

Current studies, therefore, indicate that Ara-A (vidarabine) is useful for the treatment of localized segmental herpes zoster in immunocompromised patients, especially in the older age groups and in those with underlying lymphoproliferative disease. This antiviral therapy has to be individualized, especially in younger patients, in terms of the extent of the viral infection and underlying disease, the degree of pain involved, and the duration of signs and symptoms. Presently, antiviral therapy is not recommended for otherwise healthy persons in whom herpes zoster develops, although this problem is undergoing further study.

The patient under discussion here would qualify as a candidate for treatment with Ara-A in view of her age and underlying lymphoproliferative disease even though she was not being treated with chemotherapy.

CLINICAL DIAGNOSES

Hodgkin's disease, recurrent following radiation therapy, with widespread involvement of lymph nodes, viscera, and bone marrow.

Immunodeficiency secondary to the preceding.

Disseminated mucocutaneous herpes zoster, severe, with probable widespread visceral involvement, including lungs and central nervous system.

Shock syndrome, cause undetermined, probably due to septicemia, with progressive irreversible lactic acidosis and hepatocellular damage.

PATHOLOGY PRESENTATION

Harlan D. Alpern, MD (Pathologist-in-Chief): The original right cervical lymph node biopsy at the other hospital in 1979 (Fig 4) is characterized by complete absence of sinusoids and of follicular architecture, with replacement by a polymorphous population of cells: classic Reed-Sternberg cells, an admixture of medium and small lymphocytes, large atypical mononuclear cells, benign histiocytes, and occasional eosinophils and neutrophils. These are the features of Hodgkin's disease of the mixed cellular type, which has a prognosis intermediate between nodular sclerosing and lymphocyte-predominant types on the one hand, and the lymphocyte-depletion type on the other. The Reed-Sternberg cell is required for the diagnosis of Hodgkin's disease, but it is not pathognomonic for that condition since cells resembling Reed-Sternberg cells may be seen in other benign and malignant entities, including infectious mononucleosis, measles, mycosis fungoides, and anaplastic carcinoma.[10] The Reed-Sternberg cells must be found in the characteristic environment in order to diagnose Hodgkin's disease. The nature of these cells remains controversial; originally they were believed to be derived from histiocytes. Later Lukes suggested that the cells were of lymphocytic origin which was supported by the demonstration of immunoglobulins in the cytoplasm and on the surface of the Reed-Sternberg cell.[11,12] However, Kadin[13] more recently demonstrated that cytoplasmic immunoglobulin in individual Reed-Sternberg cells is polyclonal and that in vitro the cells phagocytize exogenous immunoglobulin. These studies provide a strong argument for a histiocytic origin for the Reed-Sternberg cell.

The spleen removed at staging laparotomy from this patient showed nodules of Hodgkin's disease containing Reed-Sternberg cells; biopsies of the liver and bone marrow at that time did not demonstrate evidence of the disease, so that the patient's disease was Stage III.

At autopsy, there was a disseminated cutaneous and

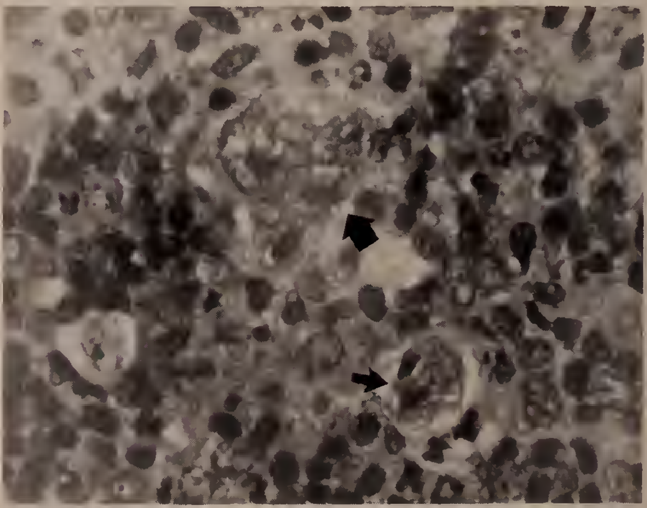

FIGURE 4. Initial cervical lymph node biopsy demonstrating Reed-Sternberg cells (arrows). (Hematoxylin and eosin stain, original magnification × 400)

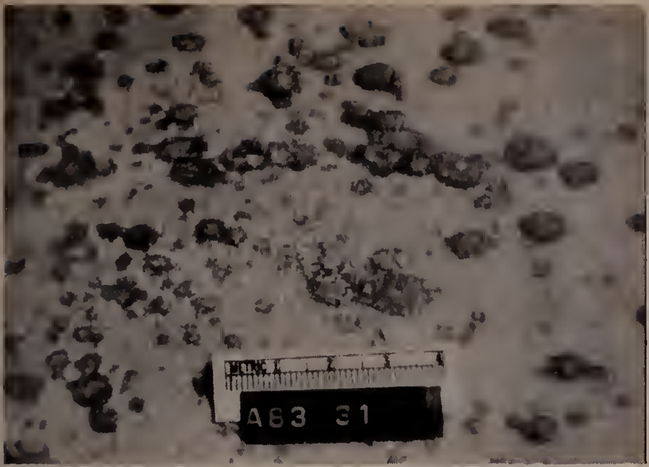

FIGURE 5. Area of vesicular dermatosis, typical of varicella-zoster virus lesions, disseminated over entire body surface.

mucous membrane vesicular dermatosis, with ulcerated lesions on the face and weeping lesions over the breast and back (Fig 5). Histologically, the lesion was an intraepidermal vesicular dermatosis (Fig 6) which results from the degeneration of infected epidermal cells and acantholysis, the destruction of the intercellular desmosomes. There were multinucleated squamous cells and nuclear inclusion bodies. The two types of degeneration that occur are: ballooning degeneration in which the cytoplasm is eosinophilic and homogeneous; and reticular degeneration in which, due to intracellular fluid accumulation, cell walls burst, producing a multilocular vesicle. The Tzanck preparation at autopsy, using the Papanicolaou stain (Fig 6), demonstrates the characteristic intranuclear inclusion bodies of herpes; the cytologic and histologic appearances of both simplex and zoster herpes viruses are identical. The antibody used in the immunoperoxidase stain identifies herpes simplex, but it does not react with the zoster virus. Molding of nuclei and glassy appearance of chromatin are characteristic of herpes infection in cytologic preparations.

The lungs at autopsy were edematous, weighing 50% more than normal. Purpuric and petechiae lesions were present on the pleural surfaces, resulting from the thrombocytopenia. On cut section of the lung, a reticulonodular pattern was identified, with numerous whitish lesions measuring up to 8 mm, varying in size, scattered throughout both lungs, representing Hodgkin's disease. On microscopic section, cellular elements were intermingled in dense fibrous connective tissue, as well as lying in alveolar air spaces. Multinucleated cells of the Reed-Sternberg type were present (Fig 7). There was a patchy pneumonia, with an inflammatory infiltrate composed primarily of neutrophils with other lymphocytes and histiocytes; no viral cytopathic changes were seen in the lung or in any of the other viscera. The disseminated herpes zoster was confined to the skin and to the mucous membranes. Culture of the lung at autopsy demonstrated group B gamma *Streptococcus* and *Staphylococcus aureus.* Intravascular fibrin thrombi were seen in the lung, compatible with the diagnosis of disseminated intravascular coagulation.

The pulmonary hilar lymph nodes were extensively involved with tumor; the histology was that of lymphocyte-depletion Hodgkin's disease, which is characteristically seen at autopsy in patients who die of what was initially a mixed cellularity type or a lymphocyte-predominant type of Hodgkin's disease. This change may occur during the course of the disease, but it may also partly be attributable to the effects of treatment. This conversion is characterized by a minor inflammatory infiltrate and a greater number of Reed-Sternberg cells as well as often abundant fibrosis.

There was involvement of the bone marrow with tumor cells and fibrosis. The liver was grossly involved by tumor, again with cellular elements and fibrous tissue; numerous tan areas grossly noted in the liver substance corresponded microscopically to profound centrilobular hepatic necrosis, attributable to shock. There were no changes in the liver suggestive of viral infection.

The left kidney was smaller than the right, probably secondary to the earlier radiation to the area of the spleen. Both showed gross evidence of Hodgkin's disease, as well as arterionephrosclerosis.

There were numerous ulcerations in the eosphagus and associated vascular thrombi and bacterial colonization. Ulceration was also present in the stomach. The duodenum

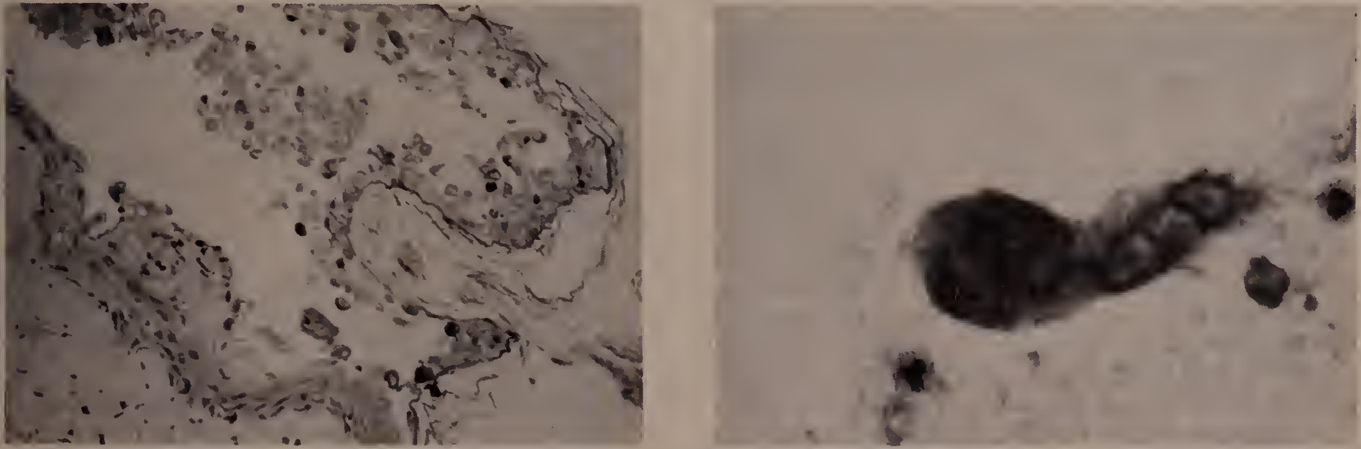

FIGURE 6. Left, vesicles resulting from ballooning of cells and reticular degeneration, with resultant destruction of intercellular attachments. (Hematoxylin and eosin stain, original magnification ×100); Right, Tzanck smear from skin vesicle—Multinucleated squamous cell with glassy chromatin, molded nuclei and intranuclear inclusions. Papanicolaou stain (original magnification ×400)

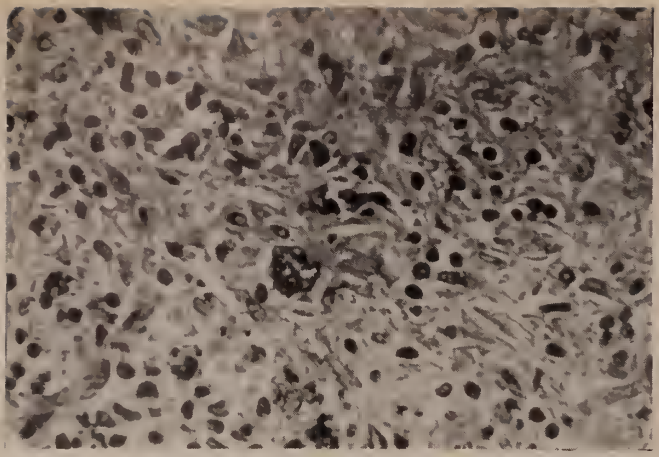

FIGURE 7. Malignant lymphoreticular infiltrate in lung, with Reed-Sternberg cells and extensive fibrosis. (Hematoxylin and eosin stain, original magnification ×250)

and the remaining small and large intestine showed the changes of ischemic enterocolitis with striking erythema, hemorrhages into the mucosa and submucosa, and ulcerations throughout the entire course of the intestine. Incidental findings included severe coronary atherosclerosis and Hashimoto's thyroiditis.

In conclusion, this patient had widely disseminated Hodgkin's disease involving numerous organs, including the lungs. In the setting of immunodeficiency, mucocutaneous herpes zoster, disseminated intravascular coagulation, and a superimposed bacterial pneumonia developed as well as a hypoperfusion of organs, with ischemic enterocolitis and hepatic necrosis, leading to her death.

Antoinette Kuzminski, MD (Attending Physician): Dr Reese, would the use of corticosteroids be contraindicated with this severity of herpes zoster?

Dr Reese: There is a belief among some infectious disease specialists that systemic steroids may increase the risk of dissemination; however, there is no clinical proof of this. In our patient's case it would be difficult to single out steroids as a contributing factor in view of the overwhelming problems that she already presented. For some years, dermatologists have used steroids in an effort to abort postherpetic neuralgia, but I think that this practice is less common now.

Donald Pollock, MD (Attending Physician): In my experience, systemic steroids are still used by dermatologists to abort postherpetic neuralgia usually in otherwise healthy patients. I have used carbidopa-levodopa (Sinemet®) with the same purpose in mind; although I have seen only a relatively few such cases in my practice, I have not seen postherpetic neuralgia develop in any of the patients.

Dr Reese: I don't think there are conclusive data on this issue but, as a physician oriented toward infectious diseases, I am inclined to avoid the use of steroids in the immunocompromised host. In this patient steroid therapy did not appear to contribute to dissemination of her herpes zoster, for dissemination was presumed to be present at the time of her follow-up visit at the other hospital, and bilateral pulmonary infiltration by tumor was also present.

But why did this patient have such a rapid downhill course and uncontrollable metabolic acidosis? Was she in shock at the time of admission here? Her blood pressure did not seem to be low during the first few hours in our hospital.

Dr Thompson: She did appear to be in some type of shock despite the normal systemic blood pressure—whether metabolically induced or septic, it is not possible to say.

Dr Reese: By strict definition, in order to have septic shock, she would have had to have positive blood cultures, and she did not have these either during life or at postmortem.

Dr Horner: In retrospect, we can learn a lesson from Dr Hartmann's comment about the nonspecificity of the pulmonary infiltrates on chest film. At the time of admission, we recognized how desperately ill the patient was; in this situation, granted that tumor and herpes dissemination were first considerations, it might have been entirely reasonable to proceed empirically with antibiotic therapy, even without positive cultures or Gram stains.

Dr Reese: I agree, and this patient was started on antibiotic as well as antiviral therapy. Of interest is the fact that the literature does not urge that a lung biopsy be performed when cutaneous dissemination of herpes zoster and bilateral infiltrations compatible with viral pneumonitis are present. I agree that, in addition to antiviral agents, we should routinely go ahead and institute broad-spectrum antibiotic therapy.

I would like to ask Dr Alpern if it is possible that early viral infection of visceral organs could occur without the characteristic histopathologic evidence. A parallel example would be instances of very early bacterial meningitis in which the spinal fluid can be normal and yet bacteria can be cultured from the fluid.

Dr Alpern: That is very unlikely. The viral changes were florid in the skin, yet no viral lesions were found in any organs, despite a careful search. In addition, viral cultures of the lung taken at autopsy were negative. The changes in the lung are those of Hodgkin's disease and of focal bacterial pneumonia.

John S. Davis, MD (Attending Physician): The extensive ulcerations of the esophagus are quite unusual; could herpes zoster have been the cause in that location?

Dr Alpern: There was no evidence of it. The diagnosis of herpetic esophagitis is generally an easy one to make.

Dr Davis: I believe that some serious change in this patient's physical status took place just about the time of her transfer from the other hospital. The enzyme profile—LDH, SGOT, SGPT—are classic for a shock-like syndrome. I wonder if she did not have a volume-depleted state before we saw her, and perhaps it was corrected by the time we first saw her. But then other changes took place that quickly became irreversible.

FINAL DIAGNOSES

Hodgkin's disease, with widespread involvement of lymph nodes, bone marrow, and viscera including lungs with superimposed focal bacterial pneumonia.

Immunodeficiency secondary to Hodgkin's disease.

Disseminated mucocutaneous herpes zoster.

Disseminated intrasvascular coagulation.

Progressive lactic acidosis.

Shock syndrome, with severe hepatic necrosis and ischemic enterocolitis.

Ulcerative esophagitis, severe.

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NEWS BRIEF

Warning on Medicaid fraud

The Office of the Deputy Attorney General for Medicaid Fraud Control has issued a warning on an individual practicing Medicaid fraud. Gilles M. Hendrick, a Haitian national, was arrested in Kings County, New York on February 17, 1984 and charged with the crime of Unauthorized Practice of Medicine—a felony which under New York law is punishable by four years in prison. Investigation also revealed that Hendrick fraudulently used the license number of a duly licensed physician in order to apply for Medicaid Provider status. On February 23rd Hendrick jumped $12,500 cash bail and fled to Haiti. According to Michael R. Berlowitz, special assistant to the attorney general, there is a danger that Hendrick may surreptitiously return to the United States and again practice medicine without a license.

Conservative management of *Citrobacter diversus* meningitis with brain abscess

Michael G. Marcus, MD, Vijaya L. Atluru, MD, Nancy E. Epstein, MD,
Robert J. Leggiadro, MD

Neonatal meningitis with brain abscess caused by the Gram-negative enteric bacillus *Citrobacter diversus* is a well-documented though uncommon clinical entity. The prognosis for infants with this central nervous system infection is poor, with one recent review reporting a case mortality rate of 34% and mental retardation in at least 74% of survivors.[1] Brain abscess formation occurs in 77% of cases of *C diversus* meningitis and contributes to mortality.[1]

We describe two infants with *C diversus* meningitis and brain abscesses who were treated successfully with intravenous moxalactam, mezlocillin, and gentamicin.

Case Reports

Case 1. A five-day-old girl was admitted to the Nassau County Medical Center (NCMC) for evaluation of fever and irritability. She had been delivered at NCMC to a 21-year-old mother (gravida 1, para 0) by spontaneous vaginal delivery at 40 weeks of gestation. Birth weight was 3.5 kg. Prenatal history and nursery stay were unremarkable except for physiologic hyperbilirubinemia, which was noted to be resolving the day before admission.

The infant was alert but irritable. Her temperature was 38.3 °C; pulse, 140 beats/min; respirations, 24/min; and BP, 59/30 mm Hg. The skin was mildly icteric. The remainder of the physical and neurologic examination was unremarkable.

Initial laboratory studies showed the following values: WBC count, 19,600/mm^3 with 60% neutrophils, 5% band forms, 27% lymphocytes, 6% monocytes, and 2% atypical lymphocytes. Hematocrit reading was 51%; hemoglobin level, 17.4 g/dL; and platelets, 260,000/mm^3. Total bilirubin level was 13.8 mg/dL, and direct bilirubin level was 1.7 mg/dL. Liver enzyme study results, urinalysis, and a chest roentgenogram were normal.

Blood, urine, umbilical, and stool cultures were negative for bacterial pathogens. Xanthochromic cerebrospinal fluid (CSF) was obtained on lumbar puncture. A cell count revealed no cells, and Gram's stain showed no organisms. Glucose level was 38 mg/dL (blood glucose level was 72 mg/dL), and the protein level was 104 mg/dL. Therapy with 5 mg/kg of intravenous gentamicin and 200 mg/kg of ampicillin daily was begun for suspected sepsis.

The child continued to be irritable, and 36 hours after admission generalized seizures developed. Serum electrolyte, calcium, and magnesium levels were normal, and treatment with phenobarbital was initiated. At this time admission CSF cultures were growing gram-negative bacilli. Daily intravenous therapy with 150 mg/kg of moxalactam following an initial dose of 100 mg/kg was started. The next day, the organism was identified as *Citrobacter diversus*, sensitive to gentamicin, moxalactam, and mezlocillin but resistant to ampicillin by Kirby-Bauer disk diffusion.[2] Ampicillin therapy was discontinued. Minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC) determinations by the macrobroth tube dilution method[3] at the Johns Hopkins Hospital Special Microbiology Laboratory in Baltimore confirmed the disk sensitivities. The MIC and MBC levels were identical for each antibiotic tested: moxalactam, 0.5 μg/mL; mezlocillin, 32 μg/mL; and gentamicin, 2 μg/mL).

The child continued to have intermittent seizure episodes, and diphenylhydantoin therapy was added. On the third hospital day, cranial computerized tomography (CT) showed two low-density lesions, both showing irregular ring enhancement on postcontrast study. The right parietal lesion was poorly defined (Fig 1), and the right posterior temporal lesion measured 18 mm in diameter. An EEG revealed frequent sharp wave discharges in the right temporoparietal region with occasional sharp wave discharge from the left hemisphere.

A lumbar puncture on the third hospital day yielded CSF with a protein level of 156 mg/dL and a glucose level of 12 mg/dL, a WBC count of 3,140/mm^3 with 96% polymorphonuclear leukocytes, and a negative Gram's stain. This fluid was sterile. Later that day, daily intravenous therapy of 300 mg/kg of mezlocillin was started because of continued lethargy and seizures and the onset of hypothermia, hypoglycemia, and irregular respirations. Neurosurgical intervention was deferred because no midline shift or hydrocephalus was discovered by a CT scan.

By the fifth hospital day, the infant's clinical condition had improved. Seizure activity had ceased, and diphenylhydantoin therapy was eventually discontinued. Serial CT scans were obtained and showed increasing abscess

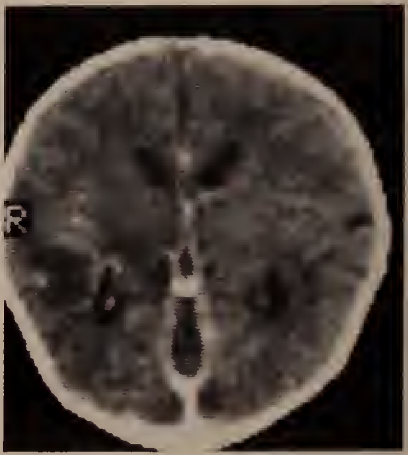

FIGURE 1. Cranial computerized tomographic scan with contrast three days after admission, showing large, low-density area in right posterior parietal region with irregular enhancement and mild dilation of lateral ventricles.

From the Departments of Pediatrics (Drs Marcus, Atluru and Leggiadro), Surgery and Neurosurgery (Dr Epstein), Nassau County Medical Center, East Meadow, NY, and SUNY-Stony Brook Health Sciences Center, Stony Brook, NY.

Address correspondence to Dr Leggiadro, MD, Director, Pediatric Infectious Disease, Nassau County Medical Center, East Meadow, NY 11554.

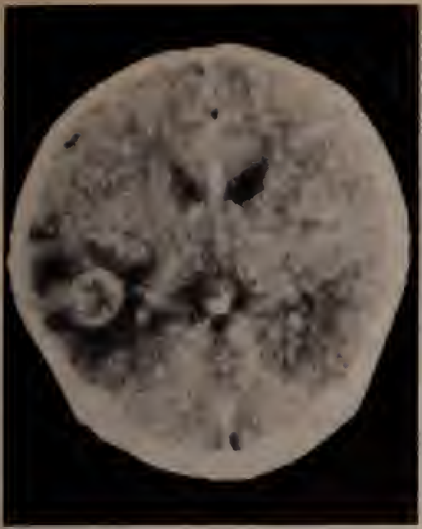

FIGURE 2. Computerized tomographic scan with contrast four weeks after admission shows ring-enhanced lesion with surrounding edema in right temporoparietal region.

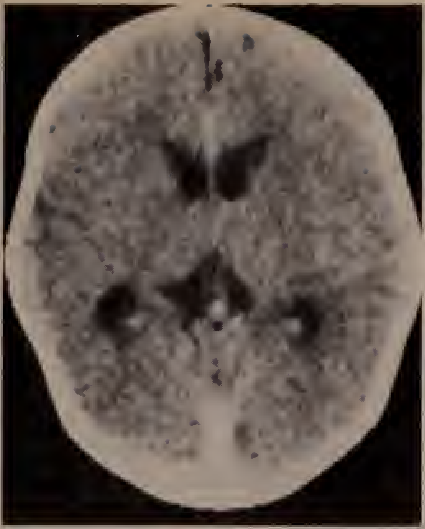

FIGURE 3. Repeat computerized tomographic scan with contrast three months after admission demonstrates complete resolution of abscess and minimal dilation of lateral ventricles.

size during the first two weeks of therapy, but the patient remained well. By the fourth week, a decrease in abscess size with postcontrast ring enhancement was noted (Fig 2). Ventricular size remained unchanged throughout the course of therapy. Follow-up scans obtained three months after her admission showed no evidence of residual abscess (Fig 3). Gentamicin therapy was continued for two weeks after the repeated lumbar puncture. The daily moxalactam dosage was increased to 300 mg/kg when she was four weeks old. Weekly complete blood cell counts, serum electrolyte, BUN, creatinine, and liver enzyme determinations, and urinalyses were performed, and results remained normal throughout the seven-week course of moxalactam and mezlocillin therapy. Treatment with these antibiotics was discontinued when a CT scan demonstrated a marked reduction in the size of both abscess cavities. Candidal diaper rash in the second week of therapy and thrush in the sixth week each resolved with topical and oral nystatin treatment, respectively. On follow-up observation, the patient showed normal development at 12 months of age, although long-term neurologic and developmental assessment is warranted.

Case 2. A six-week-old boy was admitted to NCMC for evaluation of a temperature of 39.1 °C, poor eating habits, and irritability for one day.

The boy was born to a 29-year-old mother (gravida 1, para 0) by cesarean section at 38 weeks of gestation. His mother had been treated with prednisone for three weeks before delivery for ulcerative colitis and was preeclamptic at delivery. The infant's birth weight was 2.5 kg, and there were no neonatal problems.

He was irritable, with a high-pitched cry and intermittent grunting respirations. His temperature was 38.7 °C; pulse, 148 beats/min; respirations, 44/min; and BP, 70/50 mm Hg. Head circumference was 35 cm (10th percentile). Anterior fontanelle was bulging and firm. Fundi were normal. Moro and suck reflexes were poor. The results of the remainder of the physical examination were unremarkable.

White blood cell count was 16,800/mm^3 with 74% segmented neutrophils, 13% band forms, 6% lymphocytes, and 7% monocytes. Hematocrit reading was 34%, and hemoglobin level was 11.3 mg/dL. Chest roentgenogram and urinalysis were normal. A lumbar puncture yielded turbid CSF. Cell count revealed WBCs, mostly polymorphonuclear leukocytes, in clumps. Gram's stain revealed no organisms. Protein and glucose levels were 630 mg/dL and 1.0 mg/dL, respectively.

The infant was given 300 mg of ampicillin and 7.5 mg/kg of gentamicin intravenously daily. Shortly after admission, seizure activity developed that was controlled with phenobarbital. On the first hospital day, a gram-negative bacillus, later identified as *C diversus*, was isolated from the CSF and a rectal swab. Blood, urine, and an umbilical swab were sterile. The organism was sensitive to gentamicin, moxalactam and mezlocillin by disk diffusion, and MIC and MBC determinations were identical to those of the organism of the infant girl of case 1. Because the infant's clinical condition continued to be poor, treatment with moxalactam, 200 mg/kg/day after an initial dose of 100 mg/kg, and mezlocillin, 300 mg/kg/day, was added. Ampicillin therapy was discontinued.

On the second hospital day, CSF was still turbid, with a protein level of 383 mg/dL and a glucose level of 3 mg/dL. *Citrobacter diversus* was again isolated, and CSF was bactericidal against this organism at only a 1:8 dilution.[3] The specimen was obtained five hours after administration of gentamicin and moxalactam and three hours after mezlocillin administration. A third lumbar puncture was performed one week after admission. This fluid (obtained after antibiotic administration, as described) was sterile and bactericidal against the organism in a dilution greater than or equal to 1:128.

A CT study one day after admission revealed two well-demarcated 2.5-cm lesions with ring enhancement following contrast. The lesions, compatible with abscesses, were located in the right posterior superior temporal region and in the right parietal region. The child improved during the next three weeks despite an increasing head circumference. Mild hydrocephalus was noted by scan until the fourth week, when the size of the lateral and third ventricles increased.

At this time, the child showed signs of increased intracranial pressure secondary to hydrocephalus. A ventricular tap was performed, and an opening pressure greater than 200 mm H_2O was measured. An Ommaya reservoir was inserted and the pressure relieved by daily aspiration. A CT scan after reservoir placement demonstrated a small amount of intraparenchymal blood adjacent to catheter placement in the left lateral ventricle. One week later, bloody ventricular fluid was aspirated, and a CT scan revealed blood in the lateral and third ventricles. Intramuscular vitamin K, 1 mg daily, was administered for four days, although prothrombin and activated partial thromboplastin times and fibrinogen level were normal. Platelet count was 595,000/mm^3.

Bloody ventricular fluid continued to be aspirated from the reservoir until progressive clearing began one week after gross blood was first noted. A CT scan did not reveal intraventricular blood at this time. Antibiotic therapy was discontinued the next day.

A ventriculoperitoneal shunt was placed in the left lateral ventricle three weeks after reservoir placement and after multiple sterile CSF specimens were taken. The initial ventricular fluid sample, obtained one hour after moxalactam and mezlocillin administration, had a 1:64 bactericidal titer.

Despite the resolution of the lateral ventricular size after shunting, the right temporal horn remained sequestered from the rest of the ventricular system as demonstrated by metrizamide ventriculogram. A right ventriculoperitoneal shunt was placed, and after revision, adequate decompression of the right temporal horn was effected.

Serial CT scans showed resolution of the abscesses within nine weeks of admission. Gentamicin was administered for three weeks and moxalactam and mezlocillin for eight weeks (when the minimal presence of one abscess was shown in a scan). The patient showed normal development, and both shunts continued to function well at 14 months of age, although continued neurologic follow-up observation is indicated to assess ultimate outcome.

Citrobacter diversus colonization (determined via umbilical and rectal swabs) in babies in the NCMC full-term nursery was studied on the day of the boy's admission

(21% prevalence) and weekly thereafter for nine weeks. Prevalence ranged between 7% and 22% during five weeks, before a strict cohort system was instituted. During the next four weeks, prevalence rates were 10% and 17%, before two consecutive surveys identified no colonized babies. Prevalence studies were discontinued, and no further cases of neonatal invasive *C diversus* disease were seen at NCMC during a 15-month follow-up period.

Rectal and hand cultures of nursery personnel, including house staff members, did not reveal *C diversus*, and a case-control study did not implicate a source of the organism.

DISCUSSION

The poor outcome reported with *C diversus* meningitis and brain abscess prompted our decision to use moxalactam and mezlocillin, two new beta-lactam antibiotics that penetrate the CSF, in addition to conventional gentamicin therapy in the treatment of our two patients.

Evidence of moxalactam efficacy in *C diversus* CNS infections has been reported in five patients.[4–6] A seven-week-old baby with *C diversus* meningitis and multiple cerebral abscesses was cured after seven weeks of moxalactam therapy without surgical intervention.[4] He showed normal development at eight months of age. An 890-g infant was treated with a prolonged course of moxalactam for *C diversus* meningitis and survived.[5] Schaad et al[6] reported effective moxalactam treatment of *C diversus* meningitis in three infants who were part of a clinical pharmacologic study. On the basis of the latter report and animal experiments,[7] moxalactam was selected for study in the third Neonatal Meningitis Cooperative Study Group.[6]

Limited data suggest that mezlocillin, a ureidopenicillin, may be useful in the treatment of bacterial meningitis.[8–10] It is uncertain which antibiotic or combination of antibiotics effected the favorable outcome in our patients. However, it is unlikely that eradication of *C diversus* from the CSF of our patients was due to gentamicin alone in light of that drug's poor CSF penetration.[11]

Although drug levels were not obtained, the CSF bactericidal titer of at least 1:128 after five days of therapy and ventricular fluid bactericidal titer of 1:64 on the 33rd day of therapy were compatible with sterilization of CSF and ventricular fluid in our second patient. It is interesting to note that *C diversus* grew in this patient's CSF culture when the CSF bactericidal titer was only 1:8 after one day of the three-drug regimen. A median CSF bactericidal titer of 1:64 was obtained in four rabbits with *C diversus* meningitis treated with continuous intravenous moxalactam.[7] Cerebrospinal fluid cultures were sterile in three animals at the end of nine hours of therapy.

The definitive diagnosis of brain abscess has been made easier since the advent of CT scanning.[12] In addition to providing early and more accurate diagnosis, CT scans of the brain, with injected contrast material, also allow the clinician to monitor resolution of the abscess, obviating surgical drainage in cases where abscess resolution can be documented with improvement in clinical status.[12,13]

Our patients were scanned every three to five days to evaluate changes in abscess size and concomitant mass lesion effects while receiving antimicrobial therapy. This interval was increased as clinical status improved and abscess size decreased on scan.

The seven- to eight-week course of therapy was empiric, and small residual lesions remained on scans at the conclusion of therapy in each patient. However, no parenchymal lesion was seen on scans taken six weeks and one week after completion of therapy, in the first and second patients, respectively.

A residual lesion was present on CT scan at the end of the treatment course in 10 of 20 patients with brain abscess described by Whelan and Hilal.[13] These authors believe that such lesions do not require further antibiotic treatment in most cases but recommend repeat scans one to two weeks after completion of therapy to ensure that the focus is not redeveloping. Generally, these lesions resolve in three to four months and are probably secondary to blood/brain barrier alterations.[13]

Hydrocephalus is a well-recognized complication of bacterial meningitis. However, intraventricular septation, which was responsible for the trapped right temporal horn in our second patient, is described less frequently.[14,15]

Candidal superinfection in our first patient and intraventricular bleeding in the second were possible complications of antimicrobial therapy. Superinfection[16] and coagulopathy[17] secondary to hypoprothombinemia or platelet dysfunction, resulting in bleeding, have been associated with moxalactam use.

Our experience suggests that moxalactam and mezlocillin represent important therapeutic alternatives in the therapy of *C diversus* meningitis and brain abscess, although awareness of possible adverse reactions from these drugs is essential. CT scan monitoring of abscess resolution in patients with this infection may obviate the necessity and risk of surgical intervention, although a drainage procedure is indicated in those patients with brain abscess who have a depressed sensorium and signs of increased intracranial pressure or in those who fail to respond within one week of medical therapy.[13]

Acknowledgments. Platon J. Collipp, MD, and Walter T. Hughes, MD, reviewed the manuscript, and Janice Wisniewski provided secretarial assistance.

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Resistance to calcitriol therapy in postsurgical hypoparathyroidism

KUMAR SHAH, MD, URIEL S. BARZEL, MD, ERNEST SCHWARTZ, MD,
MELVIN HORWITH, MD, ROBERT GOLDSTONE, MD

The need for pharmacologic doses of vitamin D to achieve normocalcemia is well established.[1,2] With recent advances in our understanding of vitamin D metabolism, it has been shown that in hypoparathyroidism, 1α-hydroxylation of 25 hydroxyvitamin D [25(OH)D] is defective, and there is inadequate synthesis of 1,25 dihydroxyvitamin D [$1,25(OH)_2D$].[3,4] The therapeutic success achieved with calcitriol in this condition has strengthened the belief that defective 1α-hydroxylation is the cause for apparent resistance to vitamin D in hypoparathyroidism.[5,6] We describe two adult patients who had postsurgical hypoparathyroidism and who were resistant to large doses of calcitriol or dihydrotachysterol, or both.

CASE REPORT

Case 1. A 38-year-old woman underwent a thyroidectomy for thyrotoxicosis in 1978. By the second day after surgery, her serum calcium level declined to 6.3 mg/dL and her serum phosphorus level increased to 6.8 mg/dL. Full thyroid hormone replacement was achieved with levothyroxine. Therapy with 200,000 U/day of vitamin D and 8 g/day of oral calcium carbonate failed to correct the hypocalcemia, although her serum 25(OH)D level was 73 ng/mL (normal, 10 to 30 ng/mL). The patient required intravenous calcium gluconate therapy for control of hypocalcemic symptoms.

Routine laboratory studies performed at the time the patient was receiving the replacement regimen revealed normal hemogram and normal blood chemistry values except for low serum calcium and elevated serum phosphorus levels. Parathyroid hormone was undetectable on serum radioimmunoassay study at the Mayo Clinic laboratories, Rochester, Minnesota. Serum magnesium and calcitonin levels (determined at Bio-Science Laboratory, Van Nuys, CA) were within normal limits. Serum thyroxine level was 8.8 μg/dL; plasma cortisol level, 5.2 μg/dL; and prolactin level, 29.0 ng/mL, all within normal limits. Serum B_{12} and serum folate levels were normal. Fat content of 72-hour fecal collection was normal. Latex antinuclear antibody, and antimitochondrial antibody test results were negative. A barium enema, upper gastrointestinal roentgenographic series, gallbladder roentgenographic series, and intravenous pyelogram were all normal. The patient received increasing doses of calcitriol while receiving calcium carbonate during the next two years. In doses of 1 to 4 μg/day, calcitriol failed to increase serum calcium levels. During calcitriol therapy, the fasting plasma $1,25(OH)_2D$ level was 22 pg/mL. Five hours after oral administration of 1 μg of calcitriol, the $1,25(OH)_2D$ level in plasma was 36 pg/mL (assayed by Roche Laboratories, Nutley, NJ; normal, 21 to 45 pg/mL). Serum calcium levels in the fasting state and five hours after calcitriol administration remained unchanged at 7.6 mg/dL.

Case 2. A 19-year-old woman underwent subtotal thyroidectomy for diffuse toxic goiter. After surgery her serum calcium level decreased to 6.5 mg/dL, and she had mild tetany. Oral calcium supplementation, up to 9.8 g/day as 10% calcium chloride, and up to 2 mg of dihydrotachysterol daily raised the serum calcium level to only 7.6 mg/dL at the end of one month. Hypothyroidism was treated with 0.075 mg of levothyroxine daily at three weeks and later with 0.125 mg daily. After one month, the oral calcium supplement was changed to 5 g/day of calcium carbonate, and the dihydrotachysterol dose was raised to 4 mg daily. After six months on this regimen, the serum calcium level was 7.9 mg/dL and serum phosphorus level was 5.1 mg/dL. The addition of 50 mg of hydrochlorothiazide daily elevated the calcium level further to 8.9 mg/dL.

In an attempt to substitute calcitriol for dihydrotachysterol therapy, the dihydrotachysterol dose was reduced to 1.6 mg daily, and therapy with 1 μg of calcitriol daily was begun. This resulted in a decline of serum calcium to levels as low as 6.6 mg/dL. Increasing the calcitriol dose to 2.0 μg daily, in addition to 1.6 mg of dihydrotachysterol daily and 50 mg of hydrochlorothiazide daily, resulted in a gradual elevation of serum calcium over the next two months, reaching a level of 9.7 mg/dL. At this point, the calcitriol therapy was stopped in favor of returning to single-drug therapy. The patient's condition was finally maintained with 3.6 to 4.4 mg of dihydrotachysterol daily, 2 g/day of calcium carbonate, and 50 mg of hydrochlorothiazide daily. On this regimen, serum calcium levels ranged between 8.5 and 9.2 mg/dL, and serum phosphorus levels were between 3.8 and 6.8 mg/dL. There is no clinical evidence for malabsorption in this patient, whose health was good before the onset of Graves' disease.

DISCUSSION

The usual daily vitamin D (calciferol) dosage requirement in hypoparathyroidism (1.25 to 2.5 mg, or 50,000 to 100,000 U) is high in comparison with that needed for treatment of vitamin D-deficient rickets (5 to 10 μg or 200 to 400 U).[7] That this "usual" vitamin D resistance in hypoparathyroidism is largely due to reduced renal 1α-hydroxylase activity is indicated by the finding of relatively lesser resistance to the D metabolites when used in this condition: calcitriol [$1,25(OH)_2D$] or $1\alpha(OH)D$ dosages for hypoparathyroidism average 1 to 2.5 μg/day, compared with 0.5 to 1 μg/day for rickets.[7,8] Dihydrotachysterol, which does not require 1-hydroxylation for its pharmacologic function, is effective in the treatment of hypoparathyroidism in the average dose range of 0.4 to 1 mg/day. By these criteria, the calcitriol or dihydrotachysterol dosages, or both, for our two patients were abnormally high (patient 1 had no response to 4 μg of calcitriol per day, and patient 2 had no response to 1.6 mg of dihydrotachysterol plus 1 μg of calcitriol per day). Patient 2 responded to 1.6 mg of dihydrotachysterol per day and 2 μg of calcitriol per day (equivalent to a daily dose of 5.9 μg of calcitriol), and her condition was controlled with dihydrotachysterol alone in a dosage of 3.6 to 4.4 mg/day, equivalent to 8.7 to 10.6 μg of calcitriol or 10.8 to 13.2 mg (432,000 to 528,000 U) of vitamin D_2. This latter dose of dihydrotachysterol may be compared with the dose used by Chesney et al[9] to control the serum calcium level of a child with an

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From the Departments of Medicine, Montefiore Medical Center and the Albert Einstein College of Medicine (Drs Shah and Barzel), Bronx; New York Hospital and Cornell University Medical College (Dr Horwith), Manhattan; Misericordia Hospital Medical Center and New York Medical College (Drs Schwartz and Goldstone) Bronx, New York.

Address correspondence to Dr Barzel, Professor of Medicine, Department of Medicine, Montefiore Medical Center, 111 E 210 St, Bronx, NY 10467.

idiopathic hypoparathyroidism whose condition was resistant to 5 to 6 μg/day of calcitriol therapy.

Such extreme resistance to vitamin D therapy in hypoparathyroidism is uncommon. When a patient with extreme resistance is encountered, it is necessary to rule out inadequate bioavailability of the vitamin preparation used,[10] fat malabsorption, hypomagnesemia, and coexisting medullary carcinoma of the thyroid. In patient 1, all of these factors were excluded. During vitamin D administration, the serum 25(OH)D level of 73 ng/mL was more than twice normal. Fasting $1,25(OH)_2D$ level was 22 pg/mL during calcitriol administration and rose to 36 pg/mL five hours after the oral calcitriol dose of 1 μg. These data suggest that vitamin D and calcitriol were absorbed. Thus, the continued hypocalcemia could not be the result of inadequate bioavailability of vitamin D or calcitriol. We found no evidence of renal disease. Hormonal or drug interference was considered unlikely to be the cause. Patient 1 had nondetectable circulating serum radioimmunoassayable parathyroid hormone levels.

The role of parathyroid hormone in intestinal absorption of calcium is well documented.[11] Calcium kinetic and balance studies in rats and human beings have shown that after surgical ablation of parathyroid glands, there is a considerable lag period before the injection of parathyroid hormone increases intestinal absorption of calcium.[12-14] Because the hormone stimulates production of $1,25(OH)_2D$, it is now believed that its effect on intestinal calcium absorption is probably mediated through the stimulated production of $1,25(OH)_2D$.[15]

In a recent article in which the optimal dosages of various vitamin D metabolites were compared, Okano et al[8] reported that patients with surgically induced hypoparathyroidism required, for optimal control, a higher dosage of hydroxylated vitamin D metabolites and of dihydrotachysterol than did patients with idiopathic hypoparathyroidism and pseudohypoparathyroidism. The relative resistance to calcitriol and dihydrotachysterol therapy observed in our patients and by Okano et al[8] suggests that severe vitamin D resistance in surgically induced hypoparathyroidism is due not only to depression of renal 1α-hydroxylase. We propose that absence or extremely low levels of parathyroid hormone may be the pathogenic factor, implying a synergistic effect by the hormone on vitamin metabolite action, primarily on the gut absorptive site, although we recognize that abnormality of metabolism of bone may also contribute to the final outcome. With very low parathyroid hormone levels, extremely high dosages of vitamin D, its metabolites, or dihydrotachysterol are therefore required to normalize serum calcium levels.

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Esophageal involvement in acanthosis nigricans

HERBERT DYRSZKA, MD, BHARAT SANGHAVI, MD, KUMARA PEDDAMATHAM, MD, ERNESTO CRUZ, MD

Acanthosis nigricans (AN) is a dermatosis associated with a variety of conditions. Previously reported series link 19% to 60% of AN to an underlying malignancy, usually adenocarcinoma of the stomach.[1] The classical manifestations consist of hyperkeratosis, black pigmentation, and papillomatous hyperplasia of circumscribed skin areas. In addition, involvement of the oral mucosa is well known.[1-3] However, there is little awareness of esophageal involvement. Even recent reviews of AN fail to mention mucosal changes of the esophagus.[1-3] The increasing availability of fiberoptic examinations has made the esophageal manifestations of AN more recognizable. Awareness of their appearance is a prerequisite. We report the endoscopic, histologic, and roentgenographic findings of diffuse esophageal involvement.

CASE REPORT

A 60-year-old man, a professional cello player, was admitted to the hospital with a six-week history of anorexia, vomiting, and epigastric pain after each meal. He had lost

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From the Department of Medicine, New York Medical College (Drs Dyrszka and Sanghavi), the Division of Gastroenterology (Dr Peddamatham), and the Department of Pathology (Dr Cruz), Cabrini Medical Center, New York.

Address correspondence to Dr Dyrszka, Clinical Assistant Professor, Division of Gastroenterology, Cabrini Medical Center, 227 East 19th St, New York, NY 10003.

9 kg (20 lb) during three months.

On physical examination the patient appeared anemic. There were marked verrucous proliferations around the mouth and at the perianal area. Palms and soles were hyperkeratotic. Nipples and areolas showed similar conspicuous hyperkeratosis (Fig 1). Dark hyperpigmented and hyperkeratotic areas were present in both axillas and in the left parasternal region, which the patient used for support of the cello during practice (Fig 1). The buccal and palatine mucosa showed diffuse nodular elevations of soft consistency. The color of the mucosa appeared normal.

Laboratory findings revealed a moderate hypochromic, microcytic anemia with a hemoglobin level of 8.5 g/dL. Barium studies revealed numerous round clear areas of a few millimeters' diameter in the esophagus (Fig 2). A large, irregular filling defect was noted in the antrum of the stomach.

Endoscopy of the esophagus showed diffuse fine, nodular, occasionally polyp- or villous-like projections of soft consistency (Fig 3). The color of the mucosa was normal, and the motility of the esophagus seemed undisturbed. A large fungating, ulcerated mass was noted in the antrum of the stomach. The residual gastric mucosa appeared normal.

A biopsy specimen of the esophageal lesions showed marked epithelial hyperplasia over a connective tissue core rich in capillaries (Fig 4). A biopsy specimen of the antral mass revealed a poorly differentiated adenocarcinoma.

The patient underwent a subtotal gastrectomy. Metastases were found in the regional lymph nodes. Within a week after surgery the mucosal and skin lesions became less conspicuous. Within six weeks they disappeared.

DISCUSSION

The typical skin changes of AN are usually localized in the flexure areas, particularly in the axillary region. Apart from the conspicuous verrucous proliferations at the mucocutaneous junctions, our patient showed the most typical lesions—black pigmentation and hyperkeratosis—in the area of the chest, against which his cello rested while he was playing. Pressure and friction points seem to be predilection areas for the development of the typical skin lesions.[1] Oral involvement, as seen in our patient, is found in approximately 50% of cases.[1-3] In contrast, there are only a few reports of esophageal involvement. The first endoscopic observation was published by Pasini[4] in 1950, before fiberoptic instruments were available. In 1962, Krebs[5] described the autopsy findings in a patient with esophageal involvement. The widespread manifestations of AN seen in this case were linked to a metastatic adenocarcinoma of the stomach and vitamin A deficiency. The first fiberoptic observations in two cases of AN with esophageal involvement appeared in the French literature in 1975.[6] Two additional cases were reported from Japan with emphasis on radiologic features.[7]

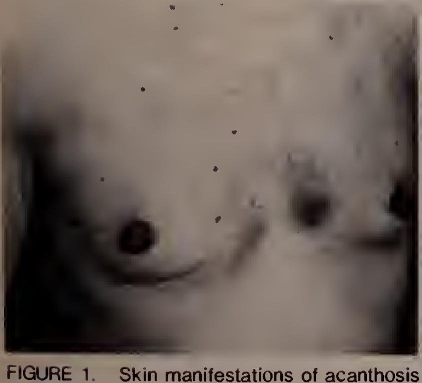

FIGURE 1. Skin manifestations of acanthosis nigricans: hyperkeratosis of nipples and areolas and areas of black pigmentation and hyperkeratosis at anterior axillary folds and in left parasternal region (pressure point during cello play).

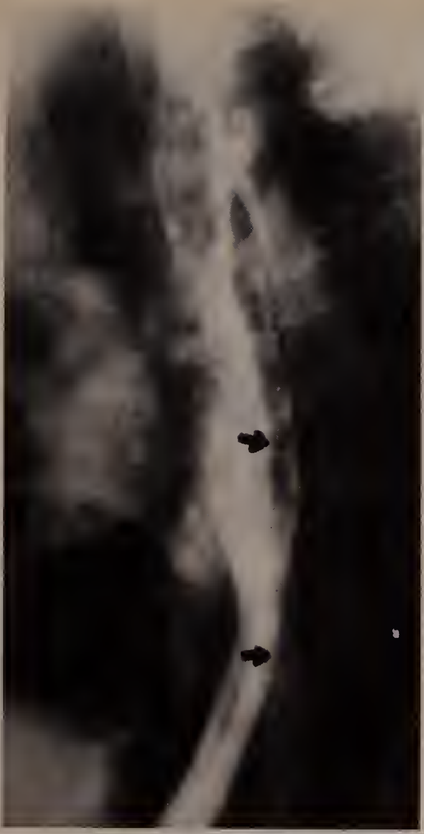

FIGURE 2. Esophagram showing small clear areas and serrated margin (arrows).

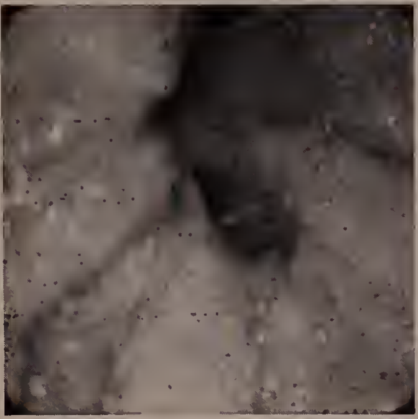

FIGURE 3. Endoscopic appearance of esophagus: diffuse nodularity scattering light reflex.

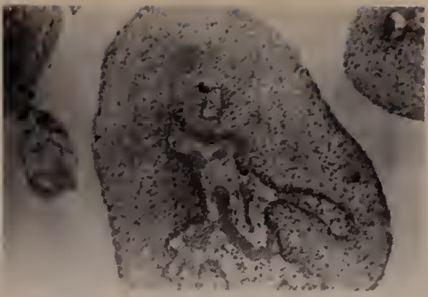

FIGURE 4. Microscopic picture of polyp-like protuberance of esophageal mucosa: papillomatous structure with marked epithelial hyperplasia and slender connective tissue core rich in capillaries (hematoxylin and eosin, original magnification × 100).

To the extent that endoscopic observations are mentioned in these reports, they resemble those made about our patient: the esophagus is diffusely lined with fine nodular, sometimes polyp-like or papillomatous proturberances of normal pink mucosal color and variable shapes. The light reflex appears scattered due to the nodular surface of the mucosa. The size of the nodules varies between 1 mm and 8 mm. The lesions are soft and detach when grasped with a biopsy forceps. Inflammatory changes are not seen. The motility of the esophagus appears unimpaired.

Roentgenographic examination of the esophagus shows small nodular clear areas, giving the mucosa a reticular or lacy appearance. The lesions are best seen in double contrast studies. The roentgenographic differential diagnosis includes moniliasis, cystic esophagitis, leukoplakia, granular peptic esophagitis, esophageal varices, and air bubbles.[7]

Upon histologic study the lesions are shown to resemble those of the oral mucosa.[2,3] Epithelial hyperplasia is the predominant characteristic. Dysplastic features and cellular atypia are not seen. The epithelium lines a slender vascular connective tissue core. Because of this papillary structure of the lesions, Mignon et al[6] referred to the esophageal changes as "diffuse esophageal papillomatosis." The histologic absence of pigment bears out the endoscopic impression that hyperpigmentation is not a feature of mucosal involvement. Although the terminology might be misleading, esophageal changes in AN are unrelated to glycogenic acanthosis of the esophagus. The latter condition is characterized by flat, whitish mucosal plaques on endoscopy. On microscopic analysis these areas show increased numbers of enlarged epithelial cells containing abundant glycogen.[8]

Our patient had no symptoms referable to the esophagus. Esophageal involvement in AN does not usually appear to cause symptoms, although mild dysphagia was reported in one case.[7]

As in our patient, underlying adenocarcinoma of the stomach was found in four of six patients described in the literature.[4-7] One patient had squamous cell carcinoma of the esophagus. In another case, no underlying malignancy or other associated condition could be found. All patients had simultaneous cutaneous manifestations of AN and oral involvement.

The true incidence of esophageal involvement in the various conditions associated with AN is unknown. It is conceivable that rare recognition rather than rare occurrence accounts for the scanty observations in the past. It is also uncertain whether isolated esophageal manifestations can occur. Acanthosis nigricans of the oral mucosa without skin lesions has been described in association with stomach cancer.[9] The increasing use of fiberoptic endoscopy may shed some light on these questions, if combined with the proper awareness of esophageal manifestations.

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Renal infarct

DAVID P. DEVER, MD, ROBERT S. DAVIS, MD

The first diagnosis of renal infarction was made by Traube in 1856.[1] Renal infarction was a difficult and infrequent diagnosis during the first half of this century.[2] In an autopsy review of 14,411 cases by Hoxie and Coggins[3] during a nine-year period there were 205 cases of renal infarction, or 1.4 percent. In only two cases was the diagnosis made antemortem. We present a case of renal infarction and demonstrate how modern radiologic techniques facilitate the confirmation of this diagnosis.

CASE REPORT

A 72-year-old white man presented to the emergency room with nausea, emesis, rigors, and a temperature of 39°C, but he was not toxic. The patient had an irregular pulse rate of 100/min and coarse bilateral basilar rales. Further examination did not reveal either flank tenderness or peritoneal signs. Laboratory evaluation disclosed a white blood cell count which was elevated (19,200/mm^3), with a shift to the left. Urinalysis showed a pH of 6, 1+ protein, 0 to 1 RBC, 0 to 1 WBC, and some epithelial cells. Urine and blood cultures were negative. Renal function was moderately impaired with a creatinine of 2.0 mg/dL. The LDH was elevated (1,166 mU/mL, normal 220 mU/mL), whereas the alkaline phosphatase was just above normal (141 mU/mL, normal 125 mU/mL). A cardiogram confirmed the presence of atrial fibrillation.

The diagnosis of renal infarction was considered, and the patient was evaluated with an intravenous urogram (Fig 1). The patient demonstrated prompt function of the right kidney with only a nephrogram on the left which became less dense on delayed films. There was no visualization of collecting structures at five hours. Renal ultrasonography revealed absence of hydronephrosis, normal renal parenchyma, and a 2-cm cyst of the lower pole of the left kidney. A renal perfusion scan and renogram demonstrated decreased perfusion of the left kidney and virtual absence of left tubular function. Computerized renal tomography, with dynamic scanning after the administration of a bolus of contrast material (Fig 2), revealed the absence of perfusion with resultant low density areas in the mid-zone and upper pole of the left kidney indicating multiple areas of segmental infarction. Although not recognized on the intravenous pyelogram or reno-

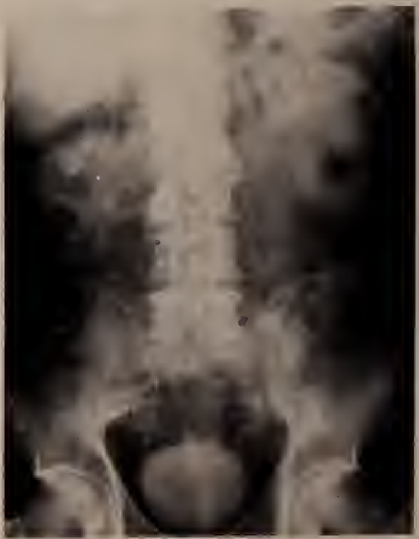

FIGURE 1. Prompt function of right kidney and only a nephrogram on the left.

From the Department of Urology, University of Rochester, School of Medicine and Dentistry, Rochester, New York.

Address correspondence to Dr Dever, Assistant Chief Resident, Department of Urology, University of Rochester, School of Medicine and Dentistry, Box 656, 601 Elmwood Ave, Rochester, NY 14642.

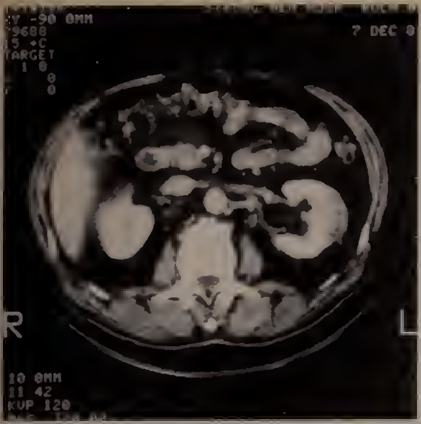

FIGURE 2. CT scan; absence of perfusion and low density areas in left kidney.

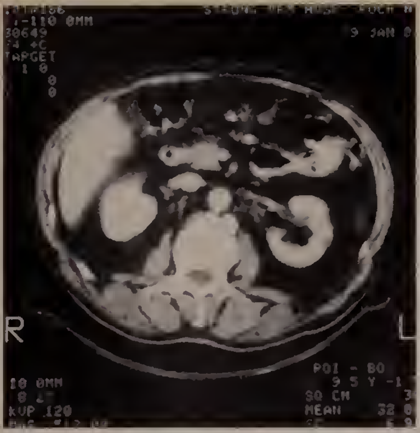

FIGURE 3. CT scan eight weeks after the infarct showing return of perfusion and some parenchymal scarring.

gram, there was also a small area of infarction in the mid-zone of the right kidney. In the area of infarction, a cortical rim of tissue was preserved suggesting collateral flow from capsular vessels.

Having established the diagnosis with these radiologic findings, treatment with anticoagulation, using heparin and later coumadin, was initiated. Cardiac ultrasonography prior to treatment revealed no remaining atrial thrombus. With anticoagulant therapy, the patient's symptoms resolved and the LDH and WBC returned to normal. The patient was discharged on a regimen of coumadin. A follow-up CT scan at eight weeks was performed (Fig 3). This demonstrated perfusion to some areas of prior infarct and some parenchymal atrophy. Currently this patient's blood pressure is 140/70 mm Hg and his serum creatinine is 1.7 mg/dL.

DISCUSSION

The etiology of renal infarction is usually emboli of cardiac origin from atrial fibrillation, mural thrombi after myocardial infarction, or rheumatic heart disease. Emboli may also originate from ulcerative aortic or renal atherosclerotic plaques and from plaques dislodged by trauma during aortic surgery, major trauma, or angiography. Renal artery thrombosis from intimal tears due to major trauma or atherosclerosis and hypercoagulable states can also result in acute renal infarction.[4]

The patient usually presents with pain in the upper abdomen or flank that subsides over two to four days.[5] Gastrointestinal symptoms of nausea, anorexia, and vomiting are common, and in half the cases the patients experience ileus. Although gross hematuria is unusual, microhematuria and albuminuria occur in over half the cases.[5] Shed renal tubular epithelial cells are often found on urinalysis.[6] Renal necrosis is heralded by an increased white cell count, fever, and release of enzymes, notably LDH, into the circulation. The increase in LDH is usually in the range of 1,000 to 2,000 units, but it has been reported as high as 7,600[7] and gradually returns to normal over several weeks.[8]

Diagnostic radiologic findings will vary with the degree of arterial occlusion. On excretory urography, the kidney with a large embolus may show nonopacification or a markedly diminished nephrogram. Segmental infarct will show localized loss on the nephrogram. Since emboli tend to migrate into larger branches with higher flow, the segmental infarct can involve the mid- or lower pole area with preservation of flow to the upper pole through its smaller dorsal branch of the renal artery.[8] Edema of the infarcted tissue may suggest a renal mass effect and may compress its adjacent calyx and infundibulum, resulting in locally impaired calyceal filling.[9] In cases of severe impairment of function, hydronephrosis can usually be excluded by delayed urogram films and renal ultrasound.[10] The latter cannot only exclude hydronephrosis but may also identify parenchymal edema of the infarcted tissue.[11]

The diagnosis of renal infarct can be further confirmed by noninvasive radiologic studies. A renal perfusion scan and renogram can identify complete or segmental lack of renal perfusion and also assist differentiation of poor function from obstruction, acute tubular necrosis, or infarction.[12] Computerized tomography, ideally with dynamic scanning after the administration of a bolus of contrast material, can confirm the diagnosis of renal infarct.[13] Areas of impaired perfusion and function can be seen on high resolution CT scans. In segmental infarcts in which capsular arteries may be intact, a rim of functioning cortex overlying the infarct may be seen on the CT scan. This "cortical rim sign" is due to preservation of cortical blood flow by anastomosis of cortical to capsular arteries.[11] Angiography, which provides the greatest degree of anatomic information on the location and size of arterial emboli, is employed only when surgical embolectomy is considered.

The treatment of renal infarct is anticoagulation or prompt surgical embolectomy, unless arterial obstruction is incomplete or patent collaterals are present.

Surgical therapy would be favored in more emergent situations, such as oliguria, anuria, or a major infarct of a solitary kidney when a maximal effort to restore renal perfusion is indicated. Anticoagulation should be considered in most cases, especially when the patient has adequate renal function following the infarct, or when the infarct is over 12 hours old. Furthermore, anticoagulation therapy has been demonstrated to be effective with resolution of fever, pain, and a decrease in white blood cell count in as little as 12 hours.[14]

Return of function may be followed by CT scan, renogram, or excretory urogram over several months. It is due to recanalization of thrombosed vessels and collateral flow from capsular vessels or other aberrant vessels.[15–17] Should an area of renal ischemia persist, renovascular hypertension may develop. The ischemic renal tissue has sufficient blood supply to circulate the pressor substances.[6,17]

We have presented a case of renal infarct and shown the role of ultrasound, renogram, and computerized tomography in ascertaining the diagnosis. Appropriate, prompt treatment may preserve renal function.

Acknowledgment. We would like to thank Dr Robert Spataro for the radiographic assistance.

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Renal artery mycotic aneurysm

Fred A. Pezzulli, MD, Frank M. Purnell, MD, Heidrun Z. Rotterdam, MD

Mycotic aneurysms of the renal artery are rare. Only 19 cases have been reported in the English language literature. We are adding a case of our own because of the good correlation of clinical, radiologic, and pathologic findings.

An analysis of all the published cases shows that the clinical manifestations are protean, and the diagnosis rests on suspicion and early angiography. When a diagnosis is made, the outcome of medical or surgical treatment is favorable.

Case Report

A 75-year-old man was admitted to Lenox Hill Hospital complaining of a recent onset of high fever and shaking chills. A chest roentgenogram was unremarkable. A blood culture was positive for *Klebsiella*. The patient was treated with intravenous fluids and antibiotics and showed improvement over the next 24 hours. Thirty hours after admission excruciating right abdominal and flank pain developed. An abdominal scout film, ultrasound, and computed tomography of the abdomen demonstrated a perinephric mass displacing the right kidney. A selective right renal arteriogram demonstrated a lobulated 1.8-cm by 0.9-cm aneurysm of a dorsal interlobar artery to the midportion of the kidney. Vessels distal to the aneurysm were sparse and there was a corresponding nephrographic defect consistent with an infarct (Fig 1). Due to the presence of septicemia and the angiographic findings, the possibility of a ruptured mycotic aneurysm of the renal artery was considered. The patient underwent surgical removal of the right kidney with an adherent perinephric hematoma. The patient recovered and was discharged in good condition.

Pathology. The resected specimen weighed 1,200 g and measured 19 × 11 × 6.5 cm. Sectioning of the kidney disclosed a perinephric hematoma varying in thickness from 1.5 to 8 cm. The kidney was of normal size. In the cortex opposite the hilum, corresponding to the location of the aneurysm seen by angiography, there was a hemorrhagic cystic lesion 1.4 cm in diameter contiguous with the perinephric hematoma. The adjacent renal cortex was infarcted (Fig 2). Under the microscope this lesion was seen to have a central lumen surrounded by lamellated fresh thrombus, pus mixed with blood, and infarcted renal cortex (Fig 3). The overlying renal capsule was ruptured and pus and blood could be seen herniating through the defect into the perirenal fat. With a van Gieson's stain for elastic fibers, a fragment of arterial wall could be demonstrated between the layer of pus and the infarcted renal tissue (Fig 4). There was no other renal pathologic condition.

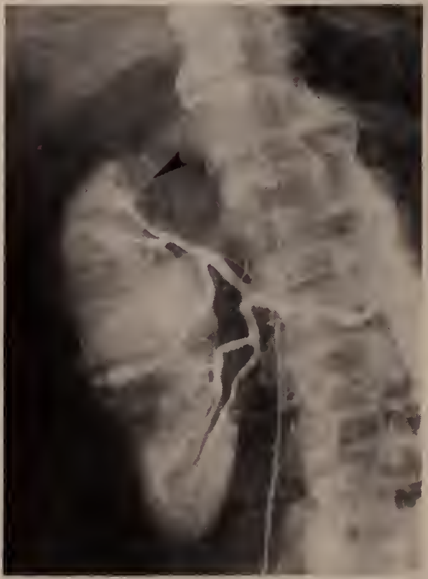

FIGURE 1. Selective right renal arteriogram. Bilocular aneurysm of an interlobar branch is demonstrated with associated nephrographic defect (small arrowhead). Supermedial nephrographic defect is due to nonfilling of an accessory renal artery (large arrowhead).

Discussion

In the first extensive review of the literature on mycotic aneurysms, Lewis and Schrager[1] in 1909 reported 97 cases, one of which occurred in a renal artery. No other information concerning the case was given. Stengel and Wolferth[2] in 1923 reviewed the world literature on mycotic aneurysms and found more than 382 aneurysms in 264 patients. Five renal artery mycotic aneurysms were found in five patients. No clinical data were submitted on these cases.

The next case was not reported until 1967 by Glass and Uson.[3] This is the first case in which clinical data are given. The patient was a 30-year-old man who died while being treated for *Staphylococcus aureus* septicemia. At autopsy an intraparenchymal renal artery mycotic

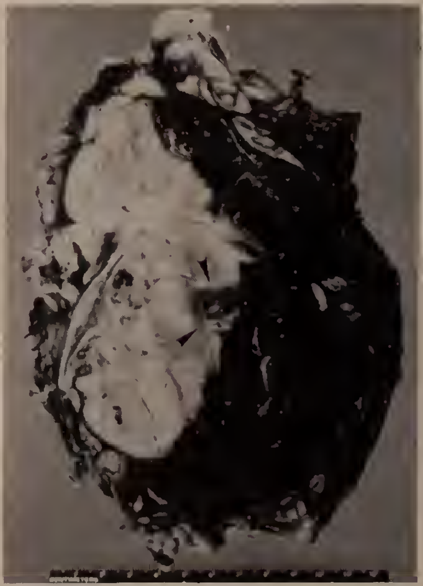

FIGURE 2. Right nephrectomy specimen. Massive perirenal hematoma surrounds normal-size kidney. Ruptured renal artery aneurysm is seen in cortex opposite hilum (arrows).

From the Departments of Radiology (Drs Pezzulli and Purnell) and Pathology (Dr Rotterdam), Lenox Hill Hospital, New York, NY.

Address correspondence to Dr Pezzulli, Associate Radiologist, Department of Radiology, Lenox Hill Hospital, 100 East 77 St, New York, NY 10021.

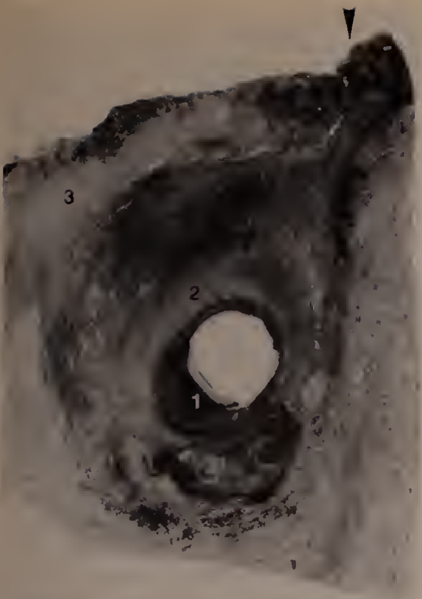

FIGURE 3. Tissue section of ruptured aneurysm. Wall is composed of fresh lamellated thrombus (1), pus mixed with blood (2), and infarcted renal cortex (3). (Hematoxylin-phloxin-safranin, original magnification × 8).

aneurysm was found. In 1969, Mundth et al[4] reported the first case of a renal artery mycotic aneurysm diagnosed antemortem. The patient was a 33-year-old man with subacute bacterial endocarditis who developed flank pain, shock, and a right loin mass. A right nephrectomy was performed and a ruptured mycotic aneurysm of an intrarenal branch of the right renal artery was found. This is also the first case of a known survival following rupture of a renal artery mycotic aneurysm. DuPreez[5] in 1969 reported the first case of a renal artery mycotic aneurysm diagnosed by angiography. Since that time, 11 additional cases have been reported, including our own, all diagnosed by angiography.[6-13]

In the 14 cases in which clinical data are available, the median age of 27.5 years (with a range of 10 months to 75 years) and male preponderance (85.7%) are similar to cases of mycotic aneurysms in general.[1,4] The high incidence of heart disease (78.6%), particularly endocarditis, is striking. This is similar to Stengel's and Wolferth's series[2] in which 86.2% of the patients had evidence of endocardial disease. Although there has been some indication that bacterial endocarditis plays a minor role in the etiology of mycotic aneurysms in general,[4,14] this series indicates that it is still a significant factor in renal artery mycotic aneurysms. This is due to renal anatomy, which would favor an embolism as the causative agent. Infection, as evidenced by fever, leukocytosis, or a positive blood culture, was present in all cases. Pain of a definite renal character was found in 42.8% of cases and a mass (either intrarenal or perinephric) was found in 28.6% of cases. These nonspecific findings focus attention on the kidneys, and may lead to the correct diagnosis. Hypertension was seen in only one case in which the blood pressure was recorded; here the aneurysm had been present several months prior to detection. The association of hypertension with atherosclerotic renal artery aneurysms is well known; it seems that the short duration of most renal artery mycotic aneurysms precludes the development of renal hypertension. Hematuria was found in all cases in which urinalysis was recorded, reflecting the tendency of mycotic aneurysms to rupture and the presence of inflammatory and ischemic changes within the kidney.

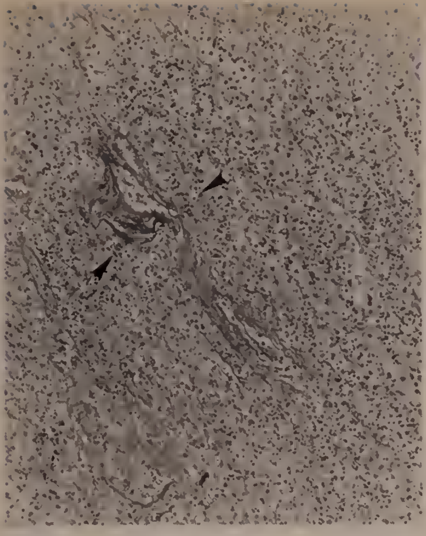

FIGURE 4. Photomicrograph of aneurysmal wall. Fragment of arterial wall (arrows) is seen amidst pus and infarcted renal cortex (van Gieson's stain, original magnification × 160).

Intravenous pyelography (IVP) was performed in eight of 14 cases and showed a variety of findings, from normal to nonfunctioning kidneys. IVP does not appear to be of any specific value in the diagnosis of renal artery mycotic aneurysms. However, angiography performed in 12 of 14 cases, always led to the correct diagnosis. In eight of 12 cases there was evidence of distal ischemia including sparsity of vessels, occlusion, infarction, or nephrographic defects. In 10 cases the aneurysms were intrarenal, in one case extrarenal, and in one case both intrarenal and extrarenal aneurysms were found. In only one case were the aneurysms multiple. Ten of the aneurysms were right-sided and nine were less than 2 cm in diameter (by direct measurement or as implied by the description). There were no specific morphologic features to suggest a mycotic cause, but two of the aneurysms had a peculiar bilocular configuration. Although there are no clear-cut criteria to differentiate a mycotic from a nonmycotic aneurysm, the aneurysms in this series tended to be small, right-sided, intrarenal, and with evidence of distal occlusion.

Surgery was performed in seven of 14 cases and ranged from incision of infarcted renal tissue with repair of the aneurysm to nephrectomy. The other cases were treated with pharmacologic agents to stabilize the patient and control the underlying infection.

The most striking feature in this series of 14 cases is that only one person died as an immediate result of the mycotic aneurysm, although 50 percent of the aneurysms ruptured. The patient recovered in every case in which the diagnosis was made antemortem, due to improved medical and surgical management. The antemortem diagnosis of renal artery and other visceral aneurysms can be made with the use of angiography, an important technique for the identification and proper treatment of these lesions.

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The Australian experiment in national health insurance—and they call it Medicare

For the past eight years, this nation has been agonizing over the best way to fund health care so that it is accessible to every Australian.

Australia has thousands of unhappy doctors. On February 1, 1984 the Federal Labor Government—in power only 11 months and led by working class-hero Bob Hawke—introduced its national health insurance scheme, Medicare.

The scheme has anguished doctors in general and the Australian Medical Association (AusMA) in particular, with leaders claiming that the right of free-enterprise private practice has been undermined and that delivery of health care will inevitably suffer. Bolstered by its members' indignation over having Medicare forced on them, the AusMA has fought on, supporting a one-day strike action by surgeons (for non-urgent cases) and backing hospital specialists who have refused to sign government contracts that would limit their income. Despite Labor attempts to assuage doctors' fears with assurances that Medicare will not sabotage private practice, physicians are reviewing the new scheme with suspicion and enmity.

Considering the volumes that have been written about the plan and the complexity of the legislation, perhaps the easiest way to summarize the *modus operandi* of Medicare is to use the words of Prime Minister Hawke in his television commercials: "At last, Australia has a simple and fair health insurance scheme that covers *every* Australian," the Prime Ministers intones. "With Medicare, everyone who can afford it contributes to the cost according to their income What could be fairer?" he asks rhetorically. In the background is a family scene of a young couple and a grandfather cuddling a baby.

The theme is simple: in an affluent society that can afford national health insurance, no one should have to worry about financial ruin due to illness or injury. Medicare will take a little extra from the high-income earners and distribute it to the two million Australians—out of 15 million—who have not had any form of health insurance for the past four years.

The commercial was a polished product of modern publicity craftsmanship, but for many it sounded uncomfortably similar to, "from each according to his abilities and to each according to his needs." Enshrined by Karl Marx, that socialist principle summarizes the basic health care philosophies of the Labor Government and the massive, powerful Australian Congress of Trade Unions (ACTU).

"DOCTORS BE WARNED"

Long before Labor was swept into power in a general election on March 5, 1983, the Labor Party and the ACTU had announced that a national health care scheme was a fundamental pylon of their platform. "Doctors be warned" was the implicit message. The AusMA, other doctors' groups and the opposition political parties have not produced any alternate schemes that would cover the two million uninsured, so the Labor Party and the trade union movement were predictably unsympathetic when doctors began to cry foul.

Prime Minister Bob Hawke appeared in commercials to smooth the way for Medicare.

"For doctors, Medicare is economic suicide," said Dr Lindsay Thompson, president of the AusMA which represents just under 50 percent of Australia's 30,000 practicing doctors. "The health and welfare of your patients, and of your families, will be sacrificed to socialist ideology," said Dr Jodhi Menon, president of the 1000-member General Practitioners' Society, in a letter sent to doctors. "Doctors will be subject to Big Brother surveillance under Medicare," he asserted repeatedly to the press, hoping that the connection with 1984 would elicit some sympathy from the public. "Medicare is the first stage of a deliberate policy to destroy the medical profession and to reduce it to being servants of the state," said a recruitment letter to doctors from the conservative opposition, the Liberal Party.

"Under Medicare, Australians will be worse off, both financially and medically. . . . It is a doctrinaire socialist theory which has failed everywhere it has been tried. . . . Medicare is an economic ploy being imposed on a trusting, unsuspecting public," wrote Dr Michael Aroney, federal secretary of the Australian Association of Surgeons, in newspaper advertisements. Doctors' comments in Letters to the Editor in major daily newspapers include: "bureaucratic monster," "crippling," "dishonest and deceitful debacle," "strong-arming," "Medi-mess," "revenge against doctors," "a doctor's nightmare."

Strong words, these, but the doctors started their battle much too late. One foot from the finishing line, Medicare was chased by an outraged AusMA that started its public campaign in earnest only three months before the scheme's inception. The AusMA's grievances have evoked little sympathy or support from the public at large, 78 percent of whom think Hawke has led his party and his country to a great comeback. Dr Neal Blewett, a former professor of political science and current Federal Minister for Health and chief architect and purveyor of Medicare, was initially low-key in his summit meetings with doctors' representatives, but as their opposition to Medicare became more strident, he struck back with strong words of his own. He accused the AusMA of being hysterical, intransigent panic merchants, unwilling to face the realities of change in modern society, and "bloody-minded" (an off-color epithet meant to imply deliberate obstructionism).

HOW IT WORKS

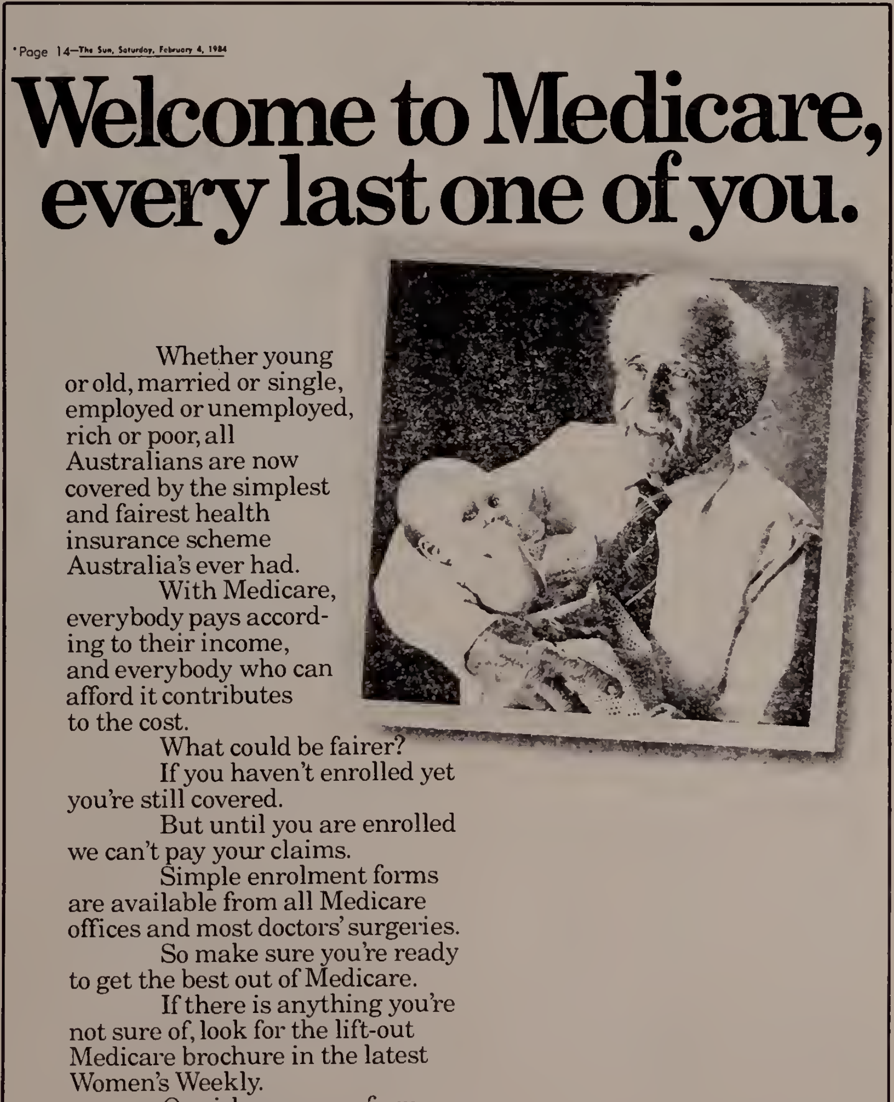
Drawing heavily from Canadian and European health care strategies but adapted to account for Australia's highly developed public hospital system, Medicare works like this. To finance health care for every citizen and resident, each employed person will have 1 percent deducted from his or her taxable income, with $700* being the maximum annual contribution. For pensioners, the unemployed, or people earning a poverty-line wage, no health tax will be levied. For example, the cut-off level for a single person is $6,700 of taxable income per year, and for a family with three children, the cut-off is $14,400.

Each patient in a public hospital is entitled to free care, regardless of the extent of tests, the number of specialists, or the amount of specialized nursing care. The catch, however, is that public patients cannot choose their own doctors and must be content with the resident medical officers and specialists assigned by the hospital.

That may sound draconian, but in Australia the public hospitals—with 80 percent of the country's beds—are regarded highly for their standard of health care delivery. Because virtually all of the leading specialists are associated with public hospitals, a patient is reasonably assured of receiving the best diagnostic, medical and surgical attention that western medicine has to offer.

Most people would not know one brain surgeon from another, but they like to have the freedom of choice. If a patient insists on having his or her own doctor, then Medicare will not cover all costs, and the patient must have private insurance to cover the extra expenses. This can become a complicated affair. Visits to the family doctor are a simple matter. Choose your own doctor, and the government will pay 85 percent of the "scheduled fee"—a sum dependent on the type of consultation and fixed by agreement between the government, the AusMA and independent arbitrators. For example, the fee for a standard consultation is $13.25, so the patient would be reimbursed $11.25 by Medicare. If a doctor charges more than the scheduled fee, then the patient still has to pay the difference, but will not be out-of-pocket by more than $10. Unlike other national health plans, Australian doctors can set any fees they please, but they risk losing business and even alienating their colleagues if charges are too steep.

The government has devised, and prefers, another method of paying doctors' fees: direct-billing. In this case, each doctor bills the government directly, accepting 85 percent of the scheduled fee and forfeiting the remaining 15 percent. Consequently, the patient does not have to hand over any money to the doctor. From the patient's point of view, this is the most attractive alternative. The government prefers direct-billing because it simplifies the paying of accounts. Direct-billing assures doctors that they



•Page 14—The Sun, Saturday, February 4, 1984

Welcome to Medicare, every last one of you.

Whether young or old, married or single, employed or unemployed, rich or poor, all Australians are now covered by the simplest and fairest health insurance scheme Australia's ever had.

With Medicare, everybody pays according to their income, and everybody who can afford it contributes to the cost.

What could be fairer?

If you haven't enrolled yet you're still covered.

But until you are enrolled we can't pay your claims.

Simple enrolment forms are available from all Medicare offices and most doctors' surgeries.

So make sure you're ready to get the best out of Medicare.

If there is anything you're not sure of, look for the lift-out Medicare brochure in the latest Women's Weekly.

Or pick up a copy from your chemist.

Medicare

Good for you, good for Australia.

The Australian government believes it pays to advertise.

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* *$1 Australian = $0.92 American*

Medicare's protagonist talks with the *Journal*

Dr Neal Blewett, Australia's Federal Minister for Health, has been the prime mover of his country's bold plan for national health care. With a PhD in economics, Dr Blewett has withstood withering blasts of political shrapnel and fall-out from doctors, but his hide seems only to toughen. Vigorous and articulate he projects a casual and friendly personal demeanor—erudite, but without a silver spoon hanging from his mouth. Exercising and swimming each day and a virtual teetotaller, he looks younger than his 50 years. His precious-little spare time is saved for his family, spent reading detective and science fiction novels or studying medieval history. He took time out to talk with the *Journal* about Medicare and other health care issues in Australia.

On Medicare's effect on private practice. "Medicare has not fundamentally changed health care from free enterprise to a socialized system. Medicare replaces private health insurance with a public health insurance system. But delivery of health care, and payment for it, remains a private fee-for-service system. Because the system in the United States is so different, I can't predict how a similar scheme would work over there. I can only say that Medicare will not have any significant impact on the private practice of medicine."

On Medicare's effect on doctors' incomes. "Overall, Medicare will have little impact on doctors' incomes. It's confusing trying to understand the objections of the General Practitioners' Society and other representatives from doctors' groups. First they say Medicare will lower incomes, and then they say it will increase incomes."

On the importance of direct-billing. "The biggest cost in delivering health insurance is in dealing with individual claims. But if doctors direct-bill the government (rather than each individual patient claiming reimbursement from the government) for all their patients, the savings are enormous. Then these savings can be passed on for improvements in hospitals, medical education, equipment, salaries and so forth."

On claims by the Australian Association of Surgeons that Medicare has failed everywhere it has been tried. "I certainly don't know where it has failed. Our closest parallel is with the Canadian system. I don't want to pretend that their system doesn't have any problems, but in large-scale surveys, it is very popular. The evidence is that national health schemes are maintained because of the popular support for them."

On Medicare's prospects for longevity. "Experience from overseas shows that once a health care scheme stabilizes—and that takes two or three years—then an incoming government is very reluctant to change it. For instance, Canada's Medicare has survived short periods of conservative rule. In the United Kingdom, their public health care is still the basic system even though the conservative government has been in power more than Labor, which introduced the scheme. This is also true in some European countries. So, I'm confident that if Medicare can survive another two years, it will remain unchanged in principle and will be the health care system at least until the end of the century."

On government contracts which hospital doctors and visiting specialists claim are income-limiting and "non-negotiable." "We have not confronted doctors with non-negotiable contracts—a lot of nonsense has been talked about on this subject. The government is laying a broad range of guidelines where these contracts can be negotiated. Doctors want to have the best of both worlds: they become ardent trade unionists when it comes to these contracts, but when we're talking about setting their scheduled fees, which are determined by an industrial arbitration process, then they claim they are not trade unionists in any sense. Well, they can't have it both ways."

On peaceful coexistence between the Australian Medical Association and the Labor Party. "Always, there are going to be tensions between representatives of the AusMA and this, or any other, government because modern government plays such a large role in providing health care. Therefore, whatever health insurance system we have, doctors' incomes are significantly underwritten by taxpayers' funds. As soon as we can resolve a couple of—what I call—'industrial-relations matters,' we will be able to peacefully coexist. But that doesn't mean we won't still have tensions, which I beleive are inevitable between doctors and governments in advanced societies."

On the financial rewards of a medical education. "I don't feel that financial returns are a part of the philosophy of medical education in Australia. Undoubtedly, however, one of the advantages is that medicine is well rewarded. It would be unrealistic to expect that young people making career decisions would not take financial reward into consideration. In the best of all possible worlds, that may not be so, but inevitably, in our society, financial reward is going to play some part."

On extra cigarette and alcohol taxes to subsidize patients with tobacco-related or alcohol-related illnesses: the "user pays" principle. "I am sympathetic to earmarking a certain percentage of excise taxes to go directly to Medicare to help pay for these patients. But the Treasury is opposed to this hypothecation of taxes. So there is a disagreement within the government on this idea. We're looking at the notion of using money—derived specifically from alcohol and tobacco excises—for public education campaigns on the dangers of tobacco and the excess use of alcohol. But a 'user-pays' principle in taxing cigarettes or alcohol is not on the horizon yet."

(*Correspondent's note: For the past three years, Australia has spent more on caring for tobacco-diseased patients than it has received from tobacco excise taxes. This is prompting support within government and health circles for specific "user pays" health taxes on tobacco.*)

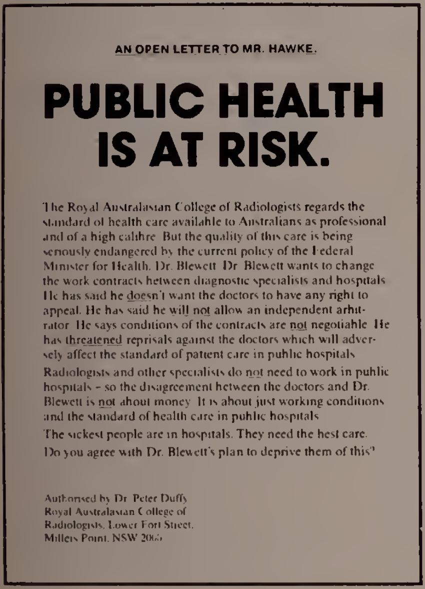
Calvin Miller, PhD

will not have any outstanding debts from non-paying patients and substantially reduces accounting costs. Nonetheless, direct-billing will reduce incomes because many doctors charge more than the scheduled fee. So, if a doctor charges $18 for a standard consultation, he or she will get a $11.25 reimbursement from the direct-billing of Medicare, a drop in fee income of 35 percent.

For hospital and medical service, a patient presents the personalized plastic health card and signs a voucher—a medical version of American Express, except that the bill is sent to the government. For services not covered by Medicare (dental, physiotherapy, chiropractic, ambulance, artificial prostheses, private-hospital accommodation and so on), people can choose among the 65 private health insurance companies.

PRECEDENTS FOR MEDICARE

Should Medicare survive the political onslaughts and become well entrenched and accepted by the public, it will end chaos in the health care system. In 1975, an earlier Labor government instituted Medibank I, a scheme that was designed to be everything that Medicare is now. But in a bizarre tale of international monetary intrigue—unrelated to medical issues—the Labor government was sacked by the Queen of England, a political situation possible only by the vestiges of colonial rule still lingering in Australia's Westminster system. The result was that the subsequent Liberal government emasculated Medibank I and replaced it with four different schemes in the ensuing seven years, each having vague traces of socialized medicine. Medicare of 1984 may not be the utopian model for health care, but it certainly is an organized attempt to establish calm and confidence from a milieu of disorder.



AN OPEN LETTER TO MR. HAWKE.

PUBLIC HEALTH IS AT RISK.

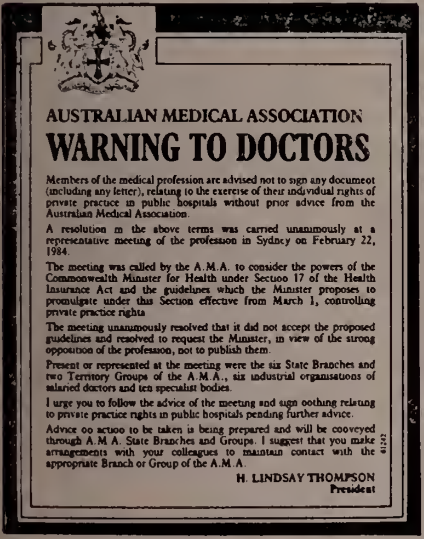
The Royal Australasian College of Radiologists regards the standard of health care available to Australians as professional and of a high calibre. But the quality of this care is being seriously endangered by the current policy of the Federal Minister for Health, Dr. Blewett. Dr. Blewett wants to change the work contracts between diagnostic specialists and hospitals. He has said he doesn't want the doctors to have any right to appeal. He has said he will not allow an independent arbitrator. He says conditions of the contracts are not negotiable. He has threatened reprisals against the doctors which will adversely affect the standard of patient care in public hospitals.

Radiologists and other specialists do not need to work in public hospitals – so the disagreement between the doctors and Dr. Blewett is not about money. It is about just working conditions and the standard of health care in public hospitals.

The sickest people are in hospitals. They need the best care.

Do you agree with Dr. Blewett's plan to deprive them of this?

Authorised by Dr. Peter Duffy
Royal Australasian College of
Radiologists, Lower Fort Street,
Millers Point, NSW 2000



AUSTRALIAN MEDICAL ASSOCIATION

WARNING TO DOCTORS

Members of the medical profession are advised not to sign any document (including any letter), relating to the exercise of their individual rights of private practice in public hospitals without prior advice from the Australian Medical Association.

A resolution in the above terms was carried unanimously at a representative meeting of the profession in Sydney on February 22, 1984.

The meeting was called by the A.M.A. to consider the powers of the Commonwealth Minister for Health under Section 17 of the Health Insurance Act and the guidelines which the Minister proposes to promulgate under this Section effective from March 1, controlling private practice rights.

The meeting unanimously resolved that it did not accept the proposed guidelines and resolved to request the Minister, in view of the strong opposition of the profession, not to publish them.

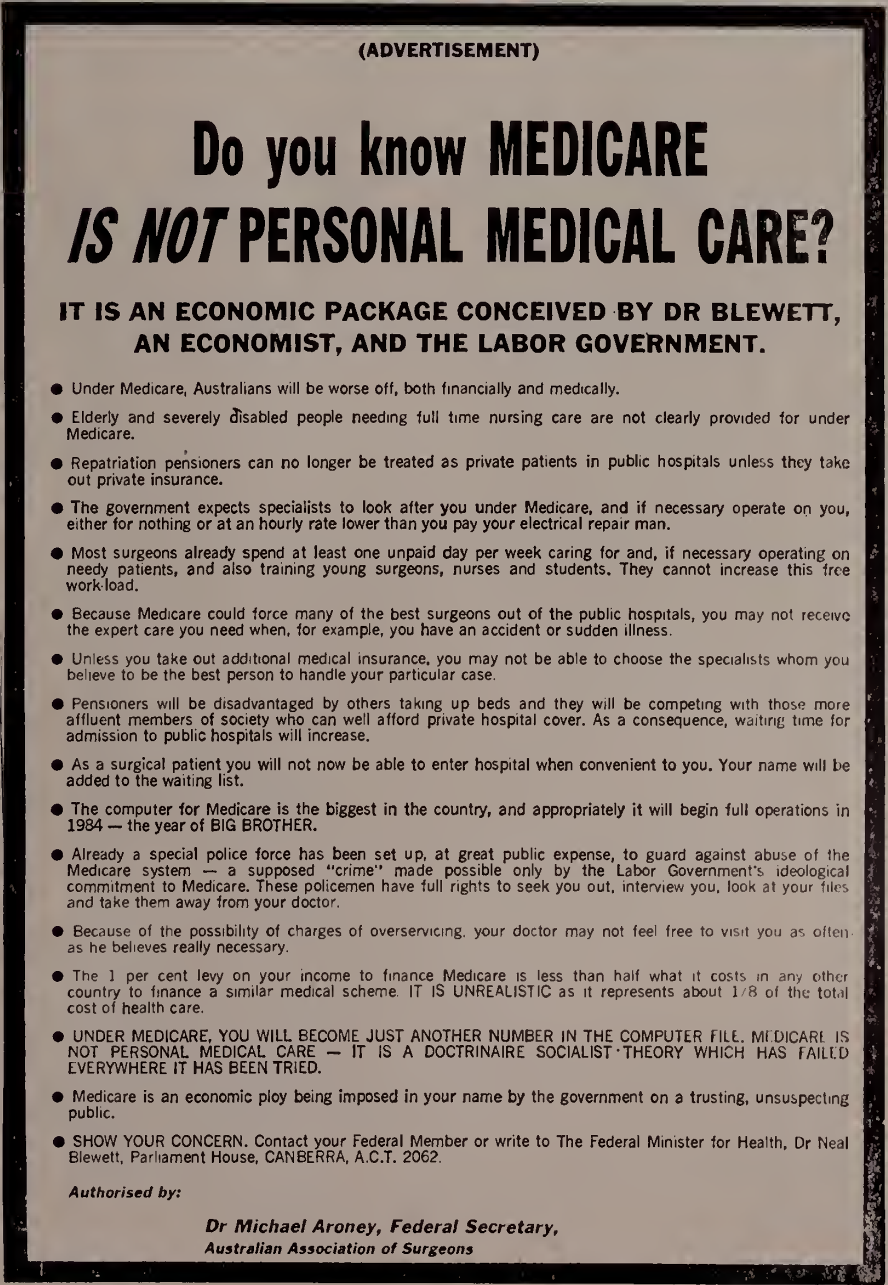
Present or represented at the meeting were the six State Branches and two Territory Groups of the A.M.A., six industrial organisations of salaried doctors and ten specialist bodies.

I urge you to follow the advice of the meeting and sign nothing relating to private practice rights in public hospitals pending further advice.

Advice on action to be taken is being prepared and will be conveyed through A.M.A. State Branches and Groups. I suggest that you make arrangements with your colleagues to maintain contact with the appropriate Branch or Group of the A.M.A.

H. LINDSAY THOMPSON
President

41242



(ADVERTISEMENT)

Do you know MEDICARE *IS NOT* PERSONAL MEDICAL CARE?

IT IS AN ECONOMIC PACKAGE CONCEIVED BY DR BLEWETT, AN ECONOMIST, AND THE LABOR GOVERNMENT.

- Under Medicare, Australians will be worse off, both financially and medically.
- Elderly and severely disabled people needing full time nursing care are not clearly provided for under Medicare.
- Repatriation pensioners can no longer be treated as private patients in public hospitals unless they take out private insurance.
- The government expects specialists to look after you under Medicare, and if necessary operate on you, either for nothing or at an hourly rate lower than you pay your electrical repair man.
- Most surgeons already spend at least one unpaid day per week caring for and, if necessary operating on needy patients, and also training young surgeons, nurses and students. They cannot increase this free work-load.
- Because Medicare could force many of the best surgeons out of the public hospitals, you may not receive the expert care you need when, for example, you have an accident or sudden illness.
- Unless you take out additional medical insurance, you may not be able to choose the specialists whom you believe to be the best person to handle your particular case.
- Pensioners will be disadvantaged by others taking up beds and they will be competing with those more affluent members of society who can well afford private hospital cover. As a consequence, waiting time for admission to public hospitals will increase.
- As a surgical patient you will not now be able to enter hospital when convenient to you. Your name will be added to the waiting list.
- The computer for Medicare is the biggest in the country, and appropriately it will begin full operations in 1984 — the year of BIG BROTHER.
- Already a special police force has been set up, at great public expense, to guard against abuse of the Medicare system — a supposed "crime" made possible only by the Labor Government's ideological commitment to Medicare. These policemen have full rights to seek you out, interview you, look at your files and take them away from your doctor.
- Because of the possibility of charges of overservicing, your doctor may not feel free to visit you as often as he believes really necessary.
- The 1 per cent levy on your income to finance Medicare is less than half what it costs in any other country to finance a similar medical scheme. IT IS UNREALISTIC as it represents about 1/8 of the total cost of health care.
- UNDER MEDICARE, YOU WILL BECOME JUST ANOTHER NUMBER IN THE COMPUTER FILE. MEDICARE IS NOT PERSONAL MEDICAL CARE — IT IS A DOCTRINAIRE SOCIALIST THEORY WHICH HAS FAILED EVERYWHERE IT HAS BEEN TRIED.
- Medicare is an economic ploy being imposed in your name by the government on a trusting, unsuspecting public.
- SHOW YOUR CONCERN. Contact your Federal Member or write to The Federal Minister for Health, Dr Neal Blewett, Parliament House, CANBERRA, A.C.T. 2062.

Authorised by:

Dr Michael Aroney, Federal Secretary,
Australian Association of Surgeons

Doctors' organizations purchased newspaper space to make their case against Medicare.

Surprisingly, the scheme is not run by the government's own Department of Health, but by a quasi-autonomous body called the Health Insurance Commission, comprised of former entrepreneurs. When Labor took office in March of 1983, the well-prepared Commission presented a comprehensive health plan in only four days, winning the right to administer Medicare.

BIG BROTHERISM?

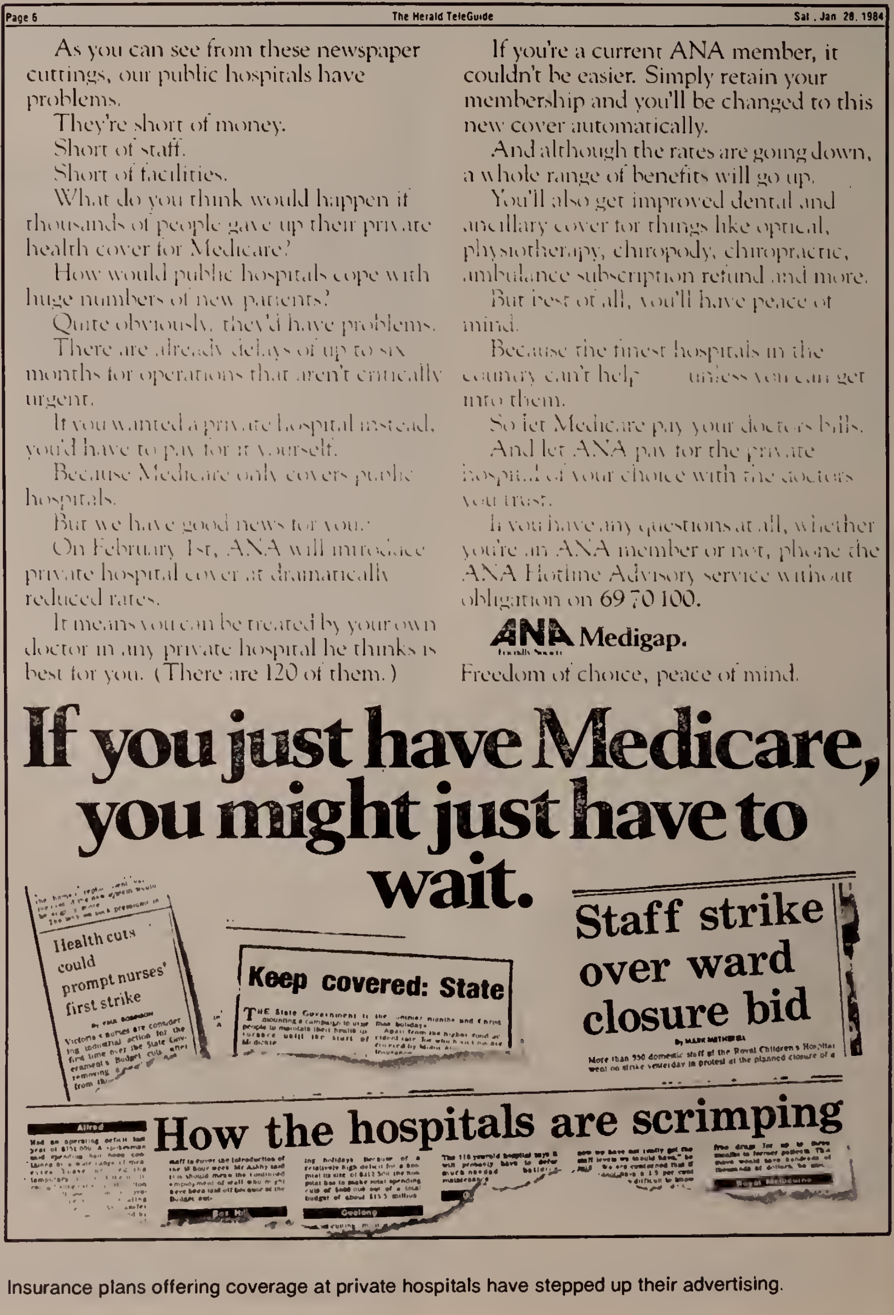
Doctors have raised several objections to the Medicare system. First, they say that Medicare will lead to unprecedented Big Brother controls over medical practice, an unhappy coincidence for Dr Blewett since this is, after all, 1984. To make certain that doctors do not file falsified direct-billing claims or over-service their patients, the government has allocated $8 million and 200 overseers armed with computers to police the medical profession. If a doctor is suspected of fraudulent claims or over-servicing, then the government has a right to seize files and interview patients.

The Labor government replies that such power is a necessity and is not a new policy—the Federal Government had this right for the past seven years under the pro-doctor Liberal Party. Policing of claims was first started in 1975 during Medibank I, when fraudulent claims and over-servicing became embarrassingly frequent. During 1983, 371 doctors were under investigation for "medi-fraud" by the Federal Department of Health, and more seriously, 54 were under investigation by the Federal Police. Medi-fraud has cost taxpayers nearly $200 million during the various health schemes of the past eight years, and the government wants to ensure that does not happen under Medicare.

Second, doctors say that Medicare will become a bureaucratic demon, splitting red tape and getting bogged down in mountains of paper work. But proponents report that the red tape will be slashed with the IBM 3084Q computer, one of the most sophisticated computer systems in the world and capable of processing the expected 265,000 claims per day.

Third, doctors suggest that if they capitulate and begin direct-billing, then not only will they lose income, but people will start a stampede for appointments seeking attention for every minor ache and scratch. Not so, replies the government, using experience from Medibank I as a precedent. During Medibank I, patients did not abuse their right to free treatment, and European and Canadian experiences have been similar, according to Dr John Deeble, one of the designers of Medicare and the ill-fated Medibank I. "The AusMA has been predicting all different kinds of financial disasters for Medicare, but we know that won't happen," Dr Deeble told the *Journal*. "Based on our experience with Medibank I and figures from Canada and Europe, people will visit their doctor about the same number of times every year. The average person visits his doctor about 5.5 times a year, which is comparable with the United States and Canada."

Dr Deeble, a senior lecturer in health economics at the Australian National University in Canberra and chairman of the Medicare Task Force, believes that Medicare will become accepted by the public and entrenched to the point that it will not be dismantled when a change of government ultimately occurs. "To become popular and stay popular, Medicare must deliver the goods as we have promised—staying within its budget, paying doctors quickly and in full, reimbursing patients promptly. This is a business organized and run by business professionals, not some vague socialist experiment run by naive egalitarians. We may not have the support of all the doctors, but the business experts who



Page 6 The Herald TeleGuide Sat., Jan 28, 1984

As you can see from these newspaper cuttings, our public hospitals have problems.

They're short of money.

Short of staff.

Short of facilities.

What do you think would happen if thousands of people gave up their private health cover for Medicare?

How would public hospitals cope with huge numbers of new patients?

Quite obviously, they'd have problems.

There are already delays of up to six months for operations that aren't critically urgent.

If you wanted a private hospital instead, you'd have to pay for it yourself.

Because Medicare only covers public hospitals.

But we have good news for you.

On February 1st, ANA will introduce private hospital cover at dramatically reduced rates.

It means you can be treated by your own doctor in any private hospital he thinks is best for you. (There are 120 of them.)

If you're a current ANA member, it couldn't be easier. Simply retain your membership and you'll be changed to this new cover automatically.

And although the rates are going down, a whole range of benefits will go up.

You'll also get improved dental and ancillary cover for things like optical, physiotherapy, chiropody, chiropractic, ambulance subscription refund and more.

But best of all, you'll have peace of mind.

Because the finest hospitals in the country can't help unless you can get into them.

So let Medicare pay your doctors bills.

And let ANA pay for the private hospital of your choice with the doctors you trust.

If you have any questions at all, whether you're an ANA member or not, phone the ANA Hotline Advisory service without obligation on 69 70 100.

ANA Medigap.

Freedom of choice, peace of mind.

If you just have Medicare, you might just have to wait.

Health cuts could prompt nurses' first strike

Keep covered: State

Staff strike over ward closure bid

How the hospitals are scrimping

Insurance plans offering coverage at private hospitals have stepped up their advertising.

Australia's hospital doctors strike, but unemployment trap looms

With the introduction of Medicare, the Australian Medical Association (AusMA) and the country's Labor Government have lapsed into a state of acrimony that has characterized their relationship during recent years, with no sign of a truce in sight. Although the current dispute centers around government-imposed contracts that limit the income of diagnostic specialists treating their private patients in public hospitals, the real issue is who shall control the delivery of health care services in Australia: the government or the doctors.

Initially a bilateral barrage of angry catchphrases, the conflict has escalated into unprecedented nationwide strikes by hospital doctors who are convinced that their independence will be permanently eroded if the government is allowed to dictate conditions on salaries and fees. Medicare and its employment contracts are an attempt to erode the private practice of medicine, the visiting specialists claim.

The transition from private to national health insurance was proceeding smoothly after Medicare's introduction on February 1. But March 1 was the deadline for the diagnosticians (pathologists and radiologists, in particular) to sign the contracts assuring that they would not charge more than the arbitrated "scheduled fee" for any type of service in public hospitals. They refused to sign. According to the Minister for Health, Dr Blewett, the contracts are imperative in order to contain the fees charged by hospital pathologists and radiologists, who have earned some notoriety because of their disproportionately high incomes. Because these specialists are treating their private patients in hospitals funded by public monies, they have a responsibility not to charge more than the scheduled fee. No free lunches at the taxpayers' expense, the government argues. The diagnostic specialists retort that most of them charge only the scheduled fee anyway, and that the contracts are a thinly guised cudgel to subjugate them. The AusMA has taken up the fight because of doctors' fears that the fee restrictions will be extended to other specialists such as anesthetists and surgeons.

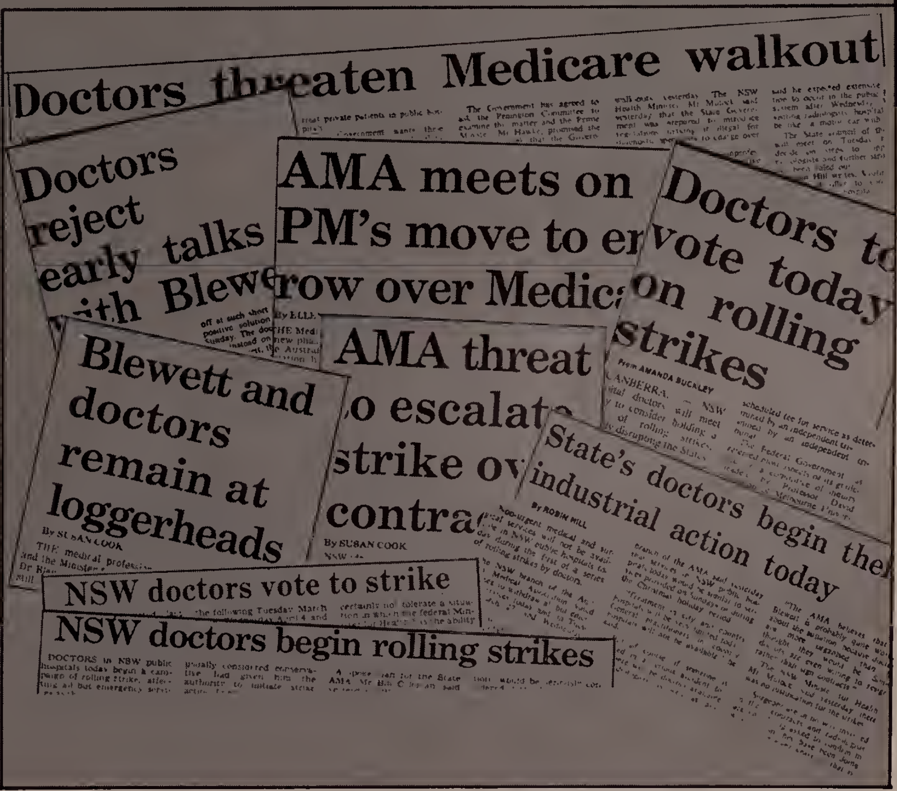
Their refusal to sign the contracts is also a protest against the infamous Section 17 of the Medicare legislation, which they find particularly offensive: that the Minister for Health has the absolute power to change conditions of the contracts without having to negotiate with the hospital doctors. Worse, Section 17 does not provide a mechanism of appeal. Such unilateral power is unprecedented and intolerable, the AusMA says. The union-oriented Labor Government would never treat any trade union so shabbily, doctors argue, and that point is compelling. Dr Blewett says that the clause actually gives the government no more power than any employer has over its employees. And after all, with the government picking up the cost of health care, the hospital doctors—both staff and visiting specialists—are indeed employees.

And so the two sides continue to bicker, with each dialectic being quickly parried by the other side. An apparently reasonable solution finally appeared in mid-March: an amendment to the Medicare law that removes the absolute power of the Minister and makes any contract alterations subject to scrutiny and approval by the Federal Parliament. Dr Blewett and AusMA officials agreed to meet. However, AusMA changed its collective mind and refused to discuss the proposal, angering Labor politicians who were beginning to see the doctors as intransigent.

As March passed, the public expected to hear of conciliation, but the AusMA and the government became more resolute in their diametrically opposed stances. In April, an uneasy moratorium was placed on the signing of the contracts pending an independent inquiry of the doctors' complaints, but industrial action was continued by some state branches of the AusMA. A solution is imperative because unless the doctors sign the employment contracts, their patients may not be eligible for Medicare reimbursement. The ramification is clear: no reimbursements, no patients.

The recourse to industrial action was the obvious next step: refuse to sign the contracts, withdraw all non-emergency services, and threaten to resign until the government capitulates. However, the doctors must tread carefully lest they fall into a trap after becoming over-confident in their industrial bargaining powers.

The government's secret weapon is unemployment. Hundreds of competent, talented doctors cannot get steady or even parttime work. Australia is overstocked with doctors who would gladly accept a permanent staff position in a hospital. A senior official in the federal Department of Health told the *Journal* that the government is gearing up to hire other doctors. While this alternative has been mooted, his information was the first hint of maneuvering behind the


Doctors threaten Medicare walkout

Doctors reject early talks

AMA meets on PM's move to e

row over Medic

Doctors to vote today on rolling strikes

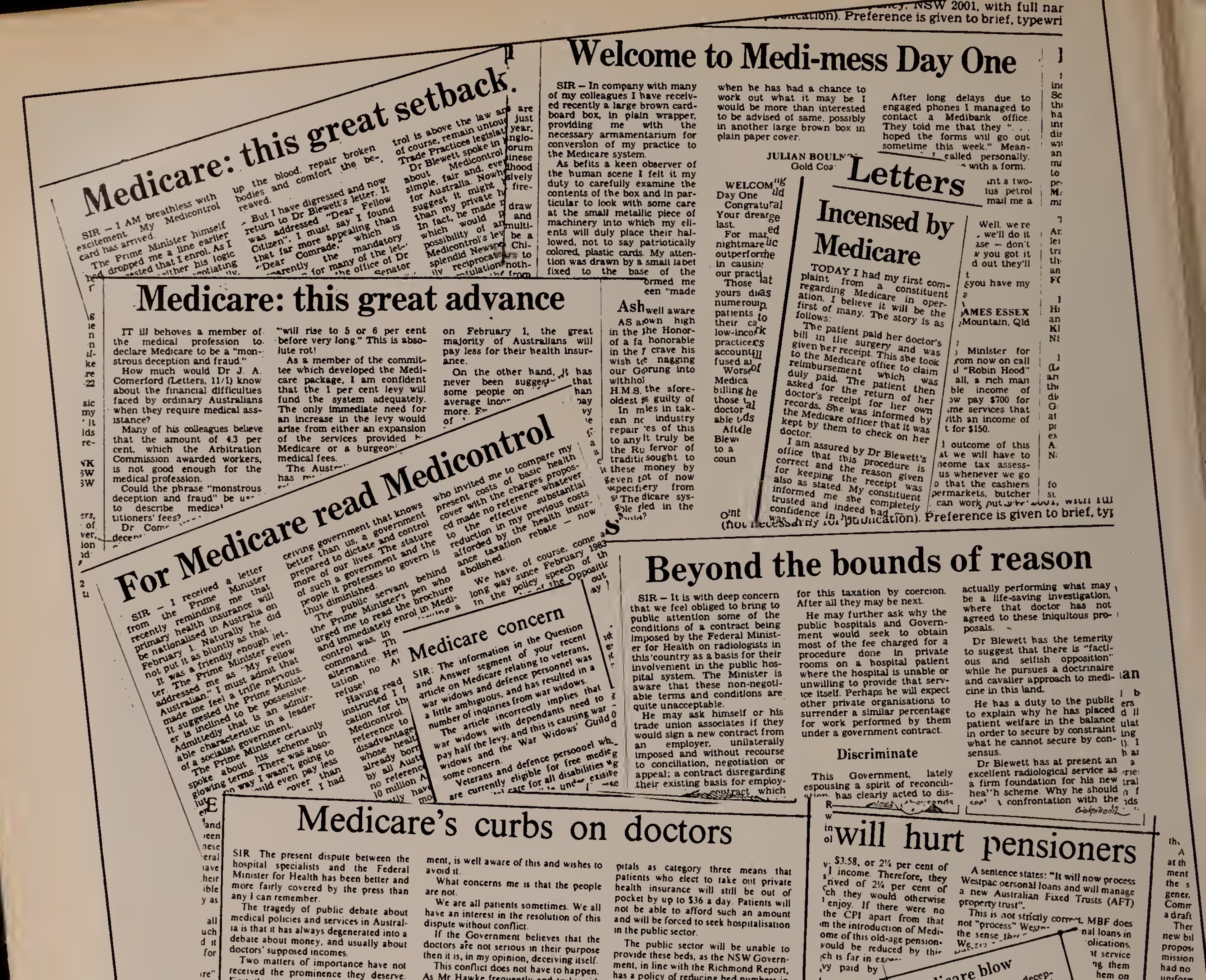
AMA threat o escalat strike o contra

Blewett and doctors remain at loggerheads

State's doctors begin the industrial action today

NSW doctors vote to strike

NSW doctors begin rolling strikes



NSW 2001, with full nar
ication). Preference is given to brief, typewri

Medicare: this great setback.

SIR – I AM breathless with excitement. My Medicontrol card has arrived.

The Prime Minister himself had dropped me a line earlier suggested that I enrol. As I neither his logic

up the blood, repair broken bodies and comfort the bereaved.

But I have digressed and now return to Dr Blewett's letter. It was addressed "Dear Fellow Citizen". I must say I found that far more appealing than "Dear Comrade," which is apparently the mandatory for many of the office of Dr Senator

trol is above the law are of course, remain untou Trade Practices legislat Dr Blewett spoke in about Medicontrol simple, fair and, eve for Australia. Nowh suggest it might than my private h In fact, he made which would possibility of an Medicontrol's lev splendid Newsp reciprocat tulation

are just year, Anglo- forum hinese hood sively fire- draw and multi- be a Chi- to noth- from

Welcome to Medi-mess Day One

SIR – In company with many of my colleagues I have received recently a large brown cardboard box, in plain wrapper, providing me with the necessary armamentarium for conversion of my practice to the Medicare system.

As befits a keen observer of the human scene I felt it my duty to carefully examine the contents of the box and in particular to look with some care at the small metallic piece of machinery into which my clients will duly place their hallowed, not to say patriotically colored, plastic cards. My attention was drawn by a small label fixed to the base of the

when he has had a chance to work out what it may be I would be more than interested to be advised of same, possibly in another large brown box in plain paper cover.

JULIAN BOULN
Gold Coa

After long delays due to engaged phones I managed to contact a Medibank office. They told me that they ". . . hoped the forms will go out sometime this week." Meanwhile I called personally. with a form.

WELCOM
Day One

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Letters

Incensed by Medicare

TODAY I had my first complaint from a constituent regarding Medicare in operation. I believe it will be the first of many. The story is as follows:

The patient paid her doctor's bill in the surgery and was given her receipt. This she took to the Medicare office to claim reimbursement which was duly paid. The patient then asked for the return of her doctor's receipt for her own records. She was informed by the Medicare officer that it was kept by them to check on her doctor.

I am assured by Dr Blewett's office that this procedure is correct and the reason given for keeping the receipt was also as stated. My constituent informed me she completely trusted and indeed had confidence in her

Well, we're we'll do it ase – don't you got it d out they'll

you have my

AMES ESSEX
Mountain, Qld

Minister for from now on call "Robin Hood" all, a rich man ble income of ow pay $700 for me services that with an income of for $150.

outcome of this at we will have to ncome tax assess- us whenever we go o that the cashiers permarkets, butcher can work out

(not necessarily for publication). Preference is given to brief, typ

Medicare: this great advance

IT ill behoves a member of the medical profession to declare Medicare to be a "monstrous deception and fraud."

How much would Dr J. A. Comerford (Letters, 11/1) know about the financial difficulties faced by ordinary Australians when they require medical assistance?

Many of his colleagues believe that the amount of 4.3 per cent, which the Arbitration Commission awarded workers, is not good enough for the medical profession.

Could the phrase "monstrous deception and fraud" be used to describe medical practitioners' fees?

Dr Com

"will rise to 5 or 6 per cent before very long." This is absolute rot!

As a member of the committee which developed the Medicare package, I am confident that the 1 per cent levy will fund the system adequately. The only immediate need for an increase in the levy would arise from either an expansion of the services provided by Medicare or a burgeoning medical fees.

The Austr

on February 1, the great majority of Australians will pay less for their health insurance.

On the other hand, it has never been suggested that some people on average inco more.

Ash

AS a own high in the Honor- of a fa honorable in the crave his wish to nagging our Gorung into withhol H.M.S. the afore- oldest is guilty of In m les in tak- ean nc industry repair es of this to any it truly be the Ru fervor of traditic sought to these money by even of now specifiery from The dicare sys- ble fled in the

For Medicare read Medicontrol

SIR – I received a letter from the Prime Minister recently reminding me that primary health insurance will be nationalised in Australia on February 1. Naturally he did not put it as bluntly as that.

It was a friendly enough letter. The Prime Minister even addressed me as "My Fellow Australian." I must admit that made me feel a trifle nervous. It suggested the Prime Minister is inclined to be possessive. Admittedly that is an admirable characteristic in a leader of a socialist government.

The Prime Minister certainly spoke about his scheme in glowing terms. There was absolutely no way I wasn't going to would even pay less cover than I had

ceiving government that knows better than us, a government prepared to dictate and control more of our lives. The stature of such a government and the people it professes to govern is thus diminished.

The public servant behind the Prime Minister's pen who urged me to read the brochure and immediately enrol in Medicontrol was, in command. alternative. tation no refuse!

Having read instructed I cation for the Medicontrol. reference to disadvantage whose health already born by all Aust no reference 10 million A

who invited me to compare my present costs of basic health cover with the charges proposed made no reference whatever to the effective substantial reduction in my previous costs afforded by the health insurance taxation rebate – now abolished.

We have, of course, come a long way since February 1983 in the policy speech of the Opposition

Medicare concern

SIR: The information in the Question and Answer segment of your recent article on Medicare relating to veterans, war widows and defence personnel was a little ambiguous, and has resulted in a number of inquiries from war widows.

The article incorrectly implies that war widows with dependants need to pay half the levy, and this is causing war widows and the War Widows' Guild some concern.

Veterans and defence personnel who are currently eligible for free medical care for all disabilities

Beyond the bounds of reason

SIR – It is with deep concern that we feel obliged to bring to public attention some of the conditions of a contract being imposed by the Federal Minister for Health on radiologists in this country as a basis for their involvement in the public hospital system. The Minister is aware that these non-negotiable terms and conditions are quite unacceptable.

He may ask himself or his trade union associates if they would sign a new contract from an employer, unilaterally imposed and without recourse to conciliation, negotiation or appeal; a contract disregarding their existing basis for employ- contract which

for this taxation by coercion. After all they may be next.

He may further ask why the public hospitals and Government would seek to obtain most of the fee charged for a procedure done in private rooms on a hospital patient where the hospital is unable or unwilling to provide that service itself. Perhaps he will expect other private organisations to surrender a similar percentage for work performed by them under a government contract.

Discriminate

This Government, lately espousing a spirit of reconciliation, has clearly acted to dis- thousands

actually performing what may be a life-saving investigation, where that doctor has not agreed to these iniquitous proposals.

Dr Blewett has the temerity to suggest that there is "factious and selfish opposition" while he pursues a doctrinaire and cavalier approach to medicine in this land.

He has a duty to the public to explain why he has placed patient welfare in the balance in order to secure by constraint what he cannot secure by consensus.

Dr Blewett has at present an excellent radiological service as a firm foundation for his new health scheme. Why he should seek a confrontation with the

Medicare's curbs on doctors

SIR The present dispute between the hospital specialists and the Federal Minister for Health has been better and more fairly covered by the press than any I can remember.

The tragedy of public debate about medical policies and services in Australia is that it has always degenerated into a debate about money, and usually about doctors' supposed incomes.

Two matters of importance have not received the prominence they deserve. First, the two seminars held by the AMA over the past month or so in NSW have

ment, is well aware of this and wishes to avoid it.

What concerns me is that the people are not.

We are all patients sometimes. We all have an interest in the resolution of this dispute without conflict.

If the Government believes that the doctors are not serious in their purpose then it is, in my opinion, deceiving itself.

This conflict does not have to happen. As Mr Hawke frequently and truly said in his ACTU days, these differences will around a table.

pitals as category three means that patients who elect to take out private health insurance will still be out of pocket by up to $36 a day. Patients will not be able to afford such an amount and will be forced to seek hospitalisation in the public sector.

The public sector will be unable to provide these beds, as the NSW Government, in line with the Richmond Report, has a policy of reducing bed numbers in the large public institutions. The result of this blunder by the governments will be that experiencing personal to find inpatient

will hurt pensioners

$3.58, or 2¼ per cent of income. Therefore, they rived of 2¼ per cent of ch they would otherwise enjoy. If there were no the CPI apart from that m the introduction of Medi- ome of this old-age pension- would be reduced by this ch is far in exc vy paid by

1.37 million 000 invalid ows receiving the other

A sentence states: "It will now process Westpac personal loans and will manage a new Australian Fixed Trusts (AFT) property trust".

This is not strictly correct. MBF does not "process" Westpac personal loans in the sense

Medicare blow

FURTHER Medicare deceptions are becoming apparent daily.

We estimate that one-third of aged pensioners attending our surgery have not been issued with Medicare plastic discs so cannot be processed in the system. All aged pensioners were promised by the Minister for Health, Dr Blewett, that they would be automatically issued with Medicare discs, a promise which clearly has not been honored

When my staff approached the matter they

Medicare: pay more for less service

SIR: Your Medical Reporter, Margaret Rice, has given a good summary of the Medicare scheme (Herald, January 24). However, it is certainly neither simple nor fairer, as the Federal Government claims.

To maintain my present level and that really is only basic right to cho for treatment to $4

Unanswered

SIR The omission of ambulance services and particularly of physiotherapy from the list of benefits one can claim under Medicare makes nonsense Federal Gove

All of us treatment

Come on, what's really up, doc?

SIR. The letters page has always been the first page my family turns to in the Herald each morning and over the past few months we have delighted in reading the letters from members of the medical profession warning us of the dangers to our bodies, as well as our souls, of Medicare.

These prolific writers, especially the members of the General Practitioners' Society, are surely wasting talents which could be well rewarded in the horror motion-picture industry by such companies as Hammer Films. The terrors that Medicare will bring to the unsuspecting peoples of Australia appear to be challenged only by Godzilla and the dreadful consequences should hospital specialists refuse to sign the new contracts that the Federal Minister for Health, Dr Blewitt, wishes to impose upon them.

While we laugh, it is nevertheless sad to realise that the medical profession is so far removed from the realities of living outside the cosy, protected world and consumer-

that the majority of people who live in this country with it voted for a Government which promised to reintroduce a tax-based, universal health insurance scheme.

Such a scheme will save money for most people, especially those who do not have the pleasure of high incomes and who have had to live in the harsh reality of reduced work opportunities and encroachments of rising costs on marginal living standards.

We should, I suppose, be used to the medical profession treating us as though we are fools. However, as we bear the cost of the expensive education medical doctors require, and as we bear the cost of providing public hospitals within which all medical practitioners have to serve their apprenticeship, I believe we are entitled to a higher level of debate and argument as compensation than we have had to date.

Consumers would appreciate reasoned argument demonstrating how much worse off patients will be by the delivery of health care under Medicare, than the emotional innuendo and

Conscripted, confused, conned

MEDICARE is an obvious misnomer. It should be Medicon – Con for confuse, Con for conscript and Con for plain old-fashioned con.

As I recall, Hayden initially promised that his baby Medibank was going to cost us 1.35 per cent on taxable income. That was back about 1973. Unfortunately the stupid LCP Opposition threw the enabling legislation out of the Senate so he simply milked the Great Cow and nobody knows how much it actually cost us.

Now we have a new socialist prophet who tells us 10-odd years on that he can do the same thing and better for a mere 1 per cent. With more than 50 years' accumulated experience of the political promises and the bureaucratic muddle, I for one don't believe him and I know full well that I do not stand alone in this belief.

For over 30 years I have rested content with the MBF and this presumably in company with a host of my fellow citizens. Now I find myself conscripted into a crummy scheme with which, as an independent person, I simply do not wish to be associated.

The medical profession is, of course, well in the pooh with this particular ministerial prophet. If we believe him it comprises a very select group of irresponsible near criminals whose one interest is money and the more the better.

Personally, I am right behind them in their determination to resist the socialist embrace.

Unlike a lot of your correspondents, I have generally a high regard for the gentlemen who weare the Hippocratic oath as I was for 31 years married to one such who happened to be a lady. As a result I often met many of them socially over a jug and listened to their endless chatter which was almost invariably "shop" – septic abortions and the like. Occasionally they did diverge.

On one such occasion one venerable old chap said, "Potentially, the most powerful trade union in this country is the AMA, but you can rely on it they will never demonstrate their strength because they are a collection of rugged individualists whom no one will ever be capable of organising."

Well, of course, that old man had never heard of Hayden or Blewett.

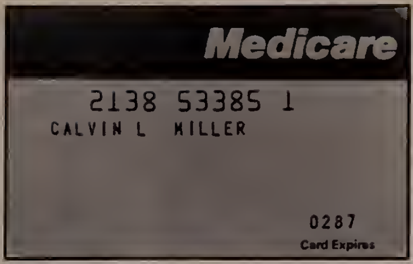
T. MILNER
Darwin

know our set-up know that this system is working. It will deliver the goods."

POLITICAL OPPOSITION

Fourth, the conservative Liberal Party claims that a levy of 1 percent on taxable income is ridiculously and deceitfully low. The difference will have to come from other revenues. They say that the Labor government is ingratiating itself with the voters, and that come the next fiscal year, the taxpayers will be faced with having to pay for a health scheme that will ultimately cost everyone more than the old systems of private health insurance combined with special government dispensations for poorer patients. To support their case, they use figures from Medibank I, which was funded by a 1.35% tax levy in 1975. However, Dr Blewett has reiterated steadfastly that 1% is sufficient, but he has also suggested that the levy may have to increase "marginally" in the next financial year. The severity of the increase is a guarded secret, but some economists have tipped that the levy will probably increase to 1.2%. Other economists say that even 1.5% is too low, and Australia will be faced with a disasterous health bill similar to England's health care debts.

Prime Minister Hawke and Dr Blewett initially claimed that nine-out-of-ten Australians would be better off under national health insurance but had to drop that ratio to two-out-of-three when the financial realities began to sink in. Medicare will be running $62 million in the red during 1985, and for the sake of longevity, the politicians must find extra revenue, particularly if the national health bill jumps unexpectedly.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SOME PHYSICIAN SUPPORT

Not all doctors are opposed to Medicare. The Doctors' Reform Society (DRS), although representing only 2 percent of the profession, has been a vocal supporter, and other doctors, even some AusMA members, see Medicare as an ideal come of age. Since its formation in 1974, the DRS has supported plans for national health insurance and has chided the AusMA for its opposition. Although it has only 300 members, the DRS claims to have extensive support throughout the profession, even among AusMA members.

Dr Jean Edwards, a general practitioner for 24 years and secretary of the DRS, direct-bills the government for all of her patients (accepting 85 percent of the scheduled fee) and feels that Medicare is good for both individual doctors and the profession. "Some doctors feel their fees should not be discounted by 15 percent, but the scheme protects doctors' incomes, and for that protection, you have to pay something," she says.

Even though Medicare's opponents have many cogent points to support their case, the winds of change are blowing fiercely, and politicians who threaten to disembowel the scheme could well be banished into the political wilderness by the voting public. Since February 1, anti-Medicare slogans from the Liberal Party have been confined to membership-drive letters sent to doctors. In recent federal by-elections and in New South Wales state elections, anti-Medicare haranguing was conspicuously avoided by opposition politicians. The AusMA, the General Practitioners' Society and other doctors' groups will have to be particularly circumspect lest their rhetoric and actions be seen as detrimental to the delivery of health care to the community. To survive, Medicare must have the cooperation of doctors. Deliberate attempts to undermine its workings will only serve to estrange doctors from a public that expects doctors to be more dedicated to the Hippocratic Oath than to the monthly bank statement.

The nation's most conservative newspaper, *The Australian*, headed by Rupert Murdoch, had this to say in editorials: "Doctors should point out Medicare's failings, but they have no right to sabotage it. The responsibility for the failure or success of Medicare rests solely with the Federal Government" (December 2, 1983), and "Like the rest of Australia, the doctors must accept that Medicare will not go away. . . . Any attempt to sabotage it would therefore be irresponsible" (January 20, 1984).

National health care schemes in western countries have been slowly gaining popular acceptance. As the concept is mooted increasingly within the United States, American physicians, politicians and health authorities will be keeping a watchful eye on the "how and why" of Medicare's success or failure.

Calvin Miller is a medical and science writer based in Taree, New South Wales. After receiving a doctorate in physiology from Monash University, Melbourne, he continued in biomedical research for several years before turning to journalism. Dr Miller has served as editor of the news features section of The Medical Journal of Australia.

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scenes to dismiss visiting specialists and to replace them with salaried staff doctors.

"If worse comes to worse and the AusMA refuses to compromise—as seems to be happening—then hospitals will simply begin hiring more staff doctors," he said, insisting on anonymity because of his politically sensitive information. "The disparity in incomes between the older, established doctors and the young doctors is tremendous. The established doctors have closed ranks over Medicare, but the younger doctors feel excluded. This hiring will take some months, and services may suffer for a little while, but plenty of out-of-work doctors are willing to live on the healthy salary that goes with a staff position (about $50,000 plus perks that can add up to $20,000). A lot of residents and interns get into radiology and pathology. The level of unemployment is such that hospitals won't have any trouble getting recruits, although remote country areas would have problems."

So opposed to the national health scheme, the specialists are actually going to precipitate a greater push toward the hiring of salaried doctors and away from the private practices in hospitals, which is exactly what the government wants. For a number of reasons, staff doctors are considerably less expensive than visiting specialists.

The doctors and their AusMA representatives have won the first few skirmishes. But if they become falsely confident, they will lose the war, ironically, as their junior colleagues begin signing employment forms.

Calvin Miller, PhD

THE PREVENTION OF THE OBSTRUCTION OF VITAL ARTERIES

By William Dock, MD, MACP. 186 pp, illustrated. St Louis, MO, Warren H Green, Inc, 1983. $42.50.

With almost missionary zeal, Dr William Dock forcefully argues for recognition and acceptance by physicians of the long accumulated evidence for the dominant role of diet in the pathogenesis of arterial obstruction. This is coupled with a plea echoed repeatedly throughout the book, for physicians to use the term "xanthosclerosis" rather than "atherosclerosis." Understanding the scientific basis and appropriateness of the former term and the inaccuracy of the latter would, in the author's opinion, enhance the physician's understanding of the causes of arterial obstruction and the measures necessary for prevention. While repeatedly emphasizing the preeminent role of diet and the importance of exercise, he also discusses the mind, emotion and other factors. Medical and surgical therapies are briefly touched upon in an interesting and philosophic manner.

By hammering away at his theme, Dock succeeds in presenting in a short, readable book, convincing evidence for the dominant role of diet in xanthosclerosis. Were all physicians who have contact with patients to read its contents, set themselves as examples, and enthusiastically and convincingly instruct their patients in preventive cardiology, there is little question that we would witness a profound decrease in the incidence of obstructive arterial disease.

Those of us who were fortunate enough to have made rounds with this master clinician and teacher will recognize the similarity between his style of writing and his style of making rounds—rapid journeys on a logical course, accented by displays of prodigious familiarity with the world's ancient and contemporary literature, medical, philosophical, and fictional. After a long career spent as a pathologist, internist, teacher, cardiologist, and researcher, Dock is able to speak with the authority, wisdom, and perspective equaled by very few in American medicine today.

The author deliberately has provided "no footnotes, no list of authors at the end of chapters and no final enumerated bibliography to identify sources." This is to allow the reader to follow the story without being diverted. Appropriate sources are cited frequently in the body of the text, however.

This book can be recommended for all physicians who treat patients, physicians who are interested in their own cardiovascular health, and scientists engaged in research into the causes and prevention of arterial obstruction. It is a short book, with many "pearls" and insights, and is written in a readable style, with wit and humor. The book also takes a few swipes along the way at special interest groups and lobbies, the Federal health establishment, and the Congress for their part in contributing to the lack of acceptance of the role of diet in xanthogenesis.

JOSEPH SCHLUGER, MD
The Long Island College Hospital
New York, NY 11201

MALIGNANT LYMPHOMAS: A PATHOLOGY ANNUAL MONOGRAPH

Edited by Sheldon C. Sommers, MD, 333 pp, illustrated. Norwalk, CN, Appleton-Century Crofts, 1983. $44.50.

"Clarity," said Ortega y Gasset, "is the courtesy of philosophers." Perhaps he should have added that clarity should also be an essential condition of any classification. Clarity, however, does not appear to be essential when dealing with the subject of lymphomas, where confusion rather than enlightenment appears to be the accepted tenet, and total obscurity its desired goal.

Fortunately, the subjects addressed in this monograph were not limited to problems of classification. This slim volume consists of six previously published articles, each written by acknowledged authorities actively involved in the practical as well as the investigative phases of hematopathology.

The first paper, "An appraisal of the working formulation of non-Hodgkin's lymphoma for clinical usage," describes in great detail a well designed study that attempts to resolve the controversy regarding the classifications of non-Hodgkin's lymphoma and to determine if this "new" classification might lead to more accurate clinical knowledge. The study, performed under the aegis of the National Cancer Institute, was retrospective and based primarily on morphologic criteria. The conclusions do not differ much from those of the Rappaport classification, except for the inclusion of some of the applicable studies since 1966.

The next paper is a provocative and stimulating study of histiocytic lesions. The authors propose a dual track of histiocytic development from one stem cell, each line being involved in different nosologic entities. The data is convincingly presented and assuredly will stimulate new studies. If the claims of the authors are confirmed, a new and exciting avenue of investigation will be opened.

An edited stenographic report of a symposium on histiocytic or large cell lymphoma was not very revealing except to reinforce the opinion that until more specific cellular labeling methods are developed, we will still rely on light microscopy with all its flaws: lack of both reproducibility and observer objectivity. What was impressive was the obvious interest and enthusiasm of the participants.

A paper on B-cell neoplasms followed. This is a most remarkable presentation. In 99 pages the authors successfully crafted a synoptic, encyclopedic presentation of the many B-cell neoplasms. Obviously they could not go into minute detail, but all aspects have been adequately described and a comprehensive list of up-to-date references is appended for those desiring more information.

A paper on primary small intestinal lymphoma, authored by an early investigator of Mediterranean-type intestinal lymphoma, is very informative. The study describes in great detail the morphologic characteristics of Mediterranean- and Western-type intestinal lymphomas as well as IgA heavy chain disease.

The final paper deals with the relationship of Hodgkin's disease and non-Hodgkin's lymphoma. All the questions that have been asked since the first description of Hodgkin's disease are mulled over in this article. Is it a lymphoma? If it is, what is its relationship to other lymphomas. If it is a lymphoma, what is the proliferating cell? What is the origin of the Reed-Sternberg cell? The problem is still in a state of flux.

The lack of a single author often results in an unevenness of style, but this is a minor point, for this monograph is replete with information that is well presented and comprehensive lists of references appended to each paper. The book is recommended for the general internist, the radiologist, the oncologist and practicing pathologists.

FIDELIO A. JIMENEZ, MD
Brooklyn Veteran's Administration and
Medical Center
New York, NY 11209

LITERATURE AND MEDICINE: IMAGES OF HEALERS. VOL 2

Edited by Anne Hudson-Jones. 160 pp, illustrated. Albany, NY, State University of New York Press, 1983. $12.95.

Both medicine and literature are concerned with the human condition. Traditionally, however, their particular perspectives have been apportioned so: medicine focuses on the objective facts of disease while literature devotes itself to the interpretation of mankind's subjective experiences. Yet for almost two decades, formal humanities programs have been infiltrating health professional education, with the past 10 years seeing a quadrupling of such programs. At last count, over 80 were in place nationwide.

This surge of cooperative effort has been motivated by both public and professional concerns that medicine, of late, has proceeded too singlemindedly in the direction of high technology and cognitive specialization, to the neglect of both the "art" of medicine and the full evocation of healing processes in the patient, which can only be energized by the affective acuity of the healer. The hope is that humanities studies will help to supply the missing elements.

Volume Two of the annual journal, *Literature and Medicine*, is devoted to the theme "Images of Healers." Anne Hudson-Jones, Associate Professor of Literature and Medicine, Institute for The Medical Humanities of the University of Texas, Medical Branch in Galveston, Texas, specifies in The Editor's Column: "We chose 'healers' rather than 'physicians' because physicians are only one kind of healer . . . And we agree to consider literature in its broadest sense so that we might include studies of film and popular culture as well as studies of poetry and fiction . . . (This volume) offers studies of many kinds of healers—physicians, surgeons, shamans, conjure men (and con men), nurses, psychoanalysts, lovers and writers—in many kinds of literature—poetry, fiction, essays, folk tales, blues song, film, television and even postage stamps."

Obviously, the very widest net has been cast by interpreting both literature and medicine with the greatest liberality. Questions of effectiveness might be raised against such loose construction of terms during early efforts to establish the legitimacy of a new field. Practitioners of medicine or of literature, already wary of this intermarriage and protective of their own delimited boundaries, might be tempted to point skeptically at this flexibility as evidence of confusion at the core. However, given the quality and well-earned reputations of the editors and contributors involved in this undertaking, it is both more generous and more apt to view this as among the bold, risky, imaginative leaps required at a frontier. Researchers in medicine, as in other fields, have traditionally defended their right to wander intuitively, unrestricted by anticipatory proofs of relevance and applicability. Serendipity (chance and the prepared mind) has been relied upon, rewardingly, to produce major advances in knowledge out of apparently unlikely couplings. This venture is worthy of similar respect and expectation.

Because this is a newly-joined field, with intimations of interdisciplinary enhancement, yet still in search of definition, inclusivity rather than exclusivity prevails. Many possible connections are being pursued simultaneously, among them healing as written of in literature, literature about healers, the act of healing via literature, healers as writers, literature as effective education for healers. The need for a forum offering freedom to explore, to experiment and to allow occasional informality of theme and format, has made the choice of the journal form most appropriate. A journal provides a triad of functions essential to a burgeoning endeavor. It serves as prod, outlet and witness to continuing developments.

This issue of *Literature and Medicine* concerns itself with literary illustrations and discussions of the healer's role. The sophisticated, experienced medical practitioner recognizes that healing (a word derived from the Anglo-Saxon root "hal," meaning "sound, healthy, whole") encompasses a great deal more than therapeutic regimens based largely on prescription remedies. Health beliefs, cultural sets, individual temperaments, ability to communicate, fears, expectations and psycho-social needs of both healer and patient all figure prominently in the process.

The articles featured in Volume Two serve to elaborate and corroborate this understanding from a new perspective, the testimony of writers and literature. Among the selections are the following: Richard Selzer, in "My Brother Shaman," writes of the "shiver of mysticism" and sense of ritual which he, as a surgeon, shares with the Buddhist shaman; Leslie Fiedler, in "Images of The Nurse in Fiction and Popular Culture," traces the literary expressions of our ambivalence toward nurses as both pure, dedicated sisters/mothers and lusty, demonic wardens/castraters; Suzanne Poirier, in "The Physician and Authority: Portraits by Four Physician-Writers," delineates the impact of individual idiosyncracy and temporal fad upon physicians' methods of relating to patients; Kathryn Montgomery Hunter, in "The Satiric Image: Healers in the *House of God*," places this modern medical students' underground favorite in the context of earlier literary satires and finds it trenchantly valid in its criticism of hospital medicine and clinical training; Loudell Snow, in "Con Men and Conjure Men: A Ghetto Image," uses blues songs, ethnic poetry, ads from ghetto newspapers and anthropological field research to elucidate the conjure men's hold, as healers, upon this needy population; D. S. Neff, in "Extraordinary Means: Healers and Healing in 'A Conversation With My Father'," discusses Grace Paley's short story about her conversation with her dying father, a physician, in which the two of them use literary argument as a surrogate for directly expressed feelings about "endings"; Nora Crow Jaffe, in "A Second Opinion on Delusions and Dreams: A Reading of Freud's Interpretation of Jensen," cautions that personal history can shape or skew the healer's professional evaluations, with Freud's interpretation of a literary work as an instructive example.

Physicians seeking to understand more fully their position within the larger sphere of healing, both as it relates to patient welfare and, reflexively, as it affects their own lives, would do well to give attention to this new journal.

Also recommended is Volume I,

edited by Kathryn A. Rabuzzi and entitled *Toward a New Discipline*, an excellent scene-setting precursor to this volume and a worthy introduction to the field in general.

Hybrids—offspring of a cross between dissimilar parents—may provide a store of raw materials from which evolutionary progress can be made, or may occur as sterile, disharmonious, ill-adapted types. The products of this union—literature and medicine—bear watching.

TALAH BELLIN, MA
State University of New York
Downstate Medical Center
New York, NY 11203

CANCER IN BRAZIL: HISTOPATHOLOGICAL DATA—1976–80

Edited by Rodolfo Brumini. 433 pp, illustrated, Rio de Janeiro, Brazil, Ministerio da Saude, 1983.

This book represents an immense effort to describe the occurrence and histopathology of 370,000 tumors in Brazil during 1976 to 1980. Some 306 laboratories participated in the data-gathering effort after receiving training in the use of the International Classification of Diseases for Oncology. The data were delivered to a coordinating center where they were reviewed for errors and processed.

The book is almost entirely in table form and clearly designed for reference use. Data for each anatomical site are presented in a similar format showing occurrence by age and sex. Next are presented the percentages of tumors at specific anatomic sites by geographic area, year, sex and age. This is followed by tables showing histologic tumor type by sex and geographic region. Several tables highlight aspects of cervical dysplasia and childhood tumors. Finally, tables are presented on the 1980 population census in Brazil.

I am sure that this book will be a valuable source of information in Brazil, but its appeal in the United States will be limited to those few who have a specific interest in comparing the United States to Brazil or in seeking hypotheses on tumor occurrence.

There are some things that make the book difficult to use. All of the text and most tables are bilingual (Portegese and English) but many tables are not.

The table of contents is virtually non-existent, although the index appears adequate. One surprising omission is data on the stage of the disease at diagnosis.

In general, for the few in the United States who may be interested, this book provides a wealth of information.

JOSEPH FELDMAN, DRPH
State University of New York
Downstate Medical Center
New York, NY 11203

CONTEMPORARY GERIATRIC MEDICINE

Vol. 1. Edited by Steven R. Gambert, MD. 412 pp, illustrated. New York, Plenum Medical Books, 1983. $49.50.

This is the first of a continuing series that attempts to summarize the current knowledge of geriatric medicine. No reference system can be expected to be state-of-the-art for geriatric medicine unless there are periodic updates. This is one of the goals of the editor of this volume.

This publication approaches geriatric medicine as do most medical texts, with chapters addressing individual organ systems. The editorial style is clear and concise, with minimal discussion of each topic. Cardiac, pulmonary, and gastrointestinal diseases are covered with an emphasis on the most common problems for this age group. Other valuable contributions to this text are chapters on rheumatology, genitourinary problems and nutritional considerations for older adults. The only chapter that seemed incomplete and cursory was that on preventive medicine and rehabilitation.

The editor is certainly well qualified to coordinate this book. He has selected a panel of contributors who will, besides acting as authors for the various chapters, participate on the editorial board for the "Contemporary" series to assure continuity for future publications. Many of these authors are recognized in geriatric medicine as valuable researchers and teachers.

Contemporary Geriatric Medicine is different from other publications in this area. The organization and abbreviated style of the book makes this a useful office reference when data is rapidly needed. The bibliographies at the end of each chapter are clearly organized so that more in-depth reading can be done. Another desirable feature of this book is that each author identifies and discusses the more common conditions practitioners encounter in their offices rather than the more esoteric diseases that rarely occur.

An example of this is the chapter on endocrinology and metabolism. The authors Barzel, Gambert and Tsitouras discuss the prevalent osteopenic bone conditions in the elderly by presenting symptoms, pathogenesis, and natural history. The diagnoses of various bone diseases are highlighted on a flow chart that serves as a quick reference. This is followed by a brief discussion on *current* treatment. The rest of the chapter discusses endocrine disorders common in the older adult population, including sexual functioning and hormonal changes associated with aging in males and females. Again, flow charts and tables are utilized. This extensive material is effectively presented in only 40 pages.

Because of the increasing number of geriatric references available, it is more difficult for the health provider to select a text that will serve his or her needs most effectively. Gambert's *Contemporary Geriatric Medicine* can be recommended for physicians who care for older adults. Because of the type of presentation, it may not give sufficient clinical details or expand on certain facts to enable other health care providers to benefit from using it as a reference. This reviewer thinks that the editor and his contributors have created a valuable book for physicians and highly recommends its use in the office.

JAMES D. LOMAX, MD
Long Island College Hospital
New York, NY 11201

CLINICAL DECISION LEVELS FOR LAB TESTS

By Bernard E. Statland, MD. 198 pp, Oradell, NJ, Medical Economics Books, 1983. $8.95.

The author is a well-known and highly regarded clinical pathologist, teacher, and writer in the field of laboratory medicine. He is experienced enough to focus on a single theme: Certain "decision levels" for various laboratory tests should generate clinical and/or laboratory action, such as "diagnosis established," "diagnosis ruled out," "next test to perform." Many physicians are not sufficiently familiar with the interpretation of laboratory results to make such decisions. No other book has this single goal and this subject is not sufficiently addressed in the medical literature or utilized in clinical practice.

Seventy-one laboratory tests are included and divided into seven categories (electrolytes, metabolites, proteins, enzymes, hormones, hematology-related tests, and therapeutic drugs). For each test, one page lists some of the common conditions in which values are increased or decreased, and gives the reference (normal) intervals (ranges). On the opposite page are listed two to four decision levels for that test and the clinical or laboratory action indicated for each level. This format is simple, concise, accurate, and clear, which makes it easy to learn the material. In fact, a third-year medical student could easily summarize all of the information on a few index cards and refer to them until quickly learned. While this may be useful, the chief value of this book is to encourage the clinician to develop and remain aware of a set of decision levels for the tests performed in the laboratory.

An important problem not addressed by the book is the frequent dilemma of borderline results, which often perplex the clinician. Thus on page 70, four decision levels are given. Creatine kinase: 10–180 U/L is given as the normal interval; less than 100 U/L "would rule out a number of entities associated with increased CK"; values above 240 U/L are "consistent with what can be expected 1–2 days after acute myocardial infarction" and a value greater than 1800 U/L "is most often seen in other pathological entities such as rhabdomyolysis, delirium tremens and status epilepticus." But in practice the range of 180–240 is often encountered and the clinician is not advised how to proceed in such an important borderline case.

Some of the author's frequently suggested actions are too vague or non-specific to be of practical use, such as "Appropriate diagnostic tests should be ordered" and "Consider various causes of increased . . ."

Such a singular and limited intent as is presented in this book will make this a "read once" type of essay rather than a frequently used "look-up" or advisory reference. While this brief and sharply focused purpose has an important advantage, the small amount of hard information provided limits the number of times the book will be used for reference and may induce many readers to borrow it from the library rather than to own it at a price of $17.50. However, it is worthwhile for all who use the laboratory to know the utility of decision levels illustrated in this book.

JACQUES WALLACH, MD
State University of New York
Downstate Medical Center
New York, NY 11203

ENJOYING LIFE WITH EMPHYSEMA

By Thomas L. Petty, MD and Louise M. Nett, RN. 189 pp, illustrated. Philadelphia, Lea & Febiger, 1983. $12.50.

This book is a short treatise containing facts and figures related to chronic obstructive pulmonary disease (COPD). It was written for patients and their families for the purpose of bringing hope, pleasure and meaning to lives of patients with COPD.

Both authors are well known in the field of pulmonary diseases, particularly COPD. They have been pioneers in the field of dealing with COPD patients and their families, and their advice is sound.

This book represents a useful addition to the medical library of the physician caring for these patients. It provides patients with an immediate explanation of their disease and its management. Most importantly, it shows patients that life with COPD is not only possible, but can also be enjoyable.

The 14 chapters discuss the anatomy of the lungs, define COPD and deal with the numerous problems that often plague patients with this disease. The glossary of terms and the excellent index are very helpful to the layman as a guide to understanding the technical jargon that pervades medical writing.

The contents of this book are clearly presented and the principles of diagnosis and management are accurate. The book's organization is excellent and its technical features uncomplicated, and thus easily understandable to the lay person. I particularly enjoyed the complete reproduction of a prize-winning article written by one of the authors' patients. It clearly addresses the problem of mobility and need for oxygen, and makes one aware of the anxieties of patients who require portable oxygen treatment for survival and well-being. Another immediately useful portion of this book is Chapter 11, Emphysema Associations. This affords the patient or his family the opportunity of contacting and joining organizations directly interested in the problem of COPD. The social and psychological support of these organizations and their ability to quell potential problems before they mushroom are immeasurable.

It is difficult to compare this book with other works of its kind because I think it has no peer. It meets all the authors' objectives and I recommend it to all patients suffering from COPD. I also think that most pulmonary physicians would benefit from reading it. They should also recommend it to patients suffering from emphysema.

JOHN A. CROCCO, MD
St. Vincent's Hospital and Medical Center
New York, NY 10011

In addition to these listings, the Journal *will publish obituaries written by physician readers. Inquiries should first be made to the Editor.*

Claire King Amyot, MD, Saratoga Springs. Died November 17, 1983; age 75. She was a 1934 alumnus of the Columbia University College of Physicians and Surgeons. Dr Amyot was a member of the Saratoga County Medical Society and the Medical Society of the State of New York.

Kazim Sinasi Apaydin, MD, Newark. Died November 17, 1983; age 56. Dr Apaydin was a 1951 graduate of Ankara University Faculty of Medicine, Ankara. He was a member of the Medical Society of the County of Wayne and the Medical Society of the State of New York.

Frederic Charles Begg, MD, Port Washington. Died December 4, 1983; age 71. He was a 1939 graduate of Harvard Medical School. Dr Begg was a Fellow of the American College of Pathologists and a Diplomate of the American Board of Pathology. He was a member of the Academy of Medicine, the New York State Society of Pathologists, the New York Pathological Society, the International Academy of Pathology, the American Society of Clinical Pathologists, the New York County Medical Society and the Medical Society of the State of New York.

Jacob C. Bernstein, MD, Greenlawn. Died November 30, 1983; age 83. He was a 1929 alumnus of McGill University Faculty of Medicine, a Fellow of the American Academy of Family Practice, a member of the Suffolk County Medical Society, and the Medical Society of the State of New York.

Roger W. Blaisdell, MD, Wellsville. Died November 19, 1983; age 78. Dr Blaisdell was a 1932 alumnus of the University of Pittsburgh School of Medicine. He was a member of the American Academy of Family Practice, the Medical Society of the County of Allegany, and the Medical Society of the State of New York.

William Leslie Bradford, MD, Rochester. Died November 12, 1983; age 85. Dr Bradford was a 1923 graduate of Washington University School of Medicine. He was a Diplomate of the American Board of Pediatrics, and a member of the American Pediatric Society, the American Academy of Pediatrics, the American Public Health Association, the Society of American Bacteriologists, the Society for Pediatric Research, the Medical Society of the County of Monroe and the Medical Society of the State of New York.

Robert Carl Brigham, MD, Lima. Died November 27, 1983; age 75. He was a 1932 graduate of the Queens University Faculty of Medicine. Dr Brigham was a member of the Medical Society of the County of Wayne and the Medical Society of the State of New York.

Orville K. Chancellor, MD, New York. Died August 7, 1982; age 76. Dr Chancellor was a 1932 alumnus of the University of Minnesota Medical School. He was a member of the New York County Medical Society and the Medical Society of the State of New York.

Fritz J. Cramer, MD, Washington, DC. Died November 18, 1982; age 83. Dr Cramer was a 1926 graduate of Cornell University Medical College. He was a member of the New York County Medical Society and the Medical Society of the State of New York.

Victor Carlo DeLuccia, MD, New York. Died December 18, 1983; age 63. Dr DeLuccia was a 1943 graduate of the State University of New York Downstate Medical Center. He was a Fellow of the American College of Surgeons, a Fellow of the American College of Chest Physicians, a Qualified Fellow of the International College of Surgeons, and a Diplomate of the American Board of Surgery and the American Board of Thoracic Surgery. His memberships included the New York Cardiological Society, the New York Society for Thoracic Surgery, the Pan American Medical Association, the Society of Thoracic Surgery, the New York County Medical Society and the Medical Society of the State of New York.

Joseph Gaar, MD, New York. Died January 5, 1983; age 75. Dr Gaar was a 1935 graduate of Kossuth Lajos Tudomanyegyetem Orvostudomanyi Fakultas, Debrecen. He was a member of the New York State Society of Anesthesiologists, the American Society of Anesthesiologists, the New York County Medical Society and the Medical Society of the State of New York.

Louis Jesse Geldzahler, MD, New York. Died December 5, 1983; age 84. Dr Geldzahler graduated in 1925 from Georgetown University School of Medicine. He was a member of the New York County Medical Society and the Medical Society of the State of New York.

James Gottesman, MD, Died December 13, 1983; age 80. He graduated from New York University College of Medicine in 1929. Dr Gottesman was a Fellow of the American Academy of Allergy and a Fellow of the American College of Allergists. He was a member of the New York County Medical Society and the Medical Society of the State of New York.

Edward B. Greenspan, MD, New York. Died November 25, 1983; age 78. Dr Greenspan was a 1930 graduate of the University of Michigan Medical School. He was a Fellow of the American College of Physicians and a member of the Academy of Medicine, the New York County Medical Society and the Medical Society of the State of New York.

Wilbur George Holz, MD, Valley Stream. Died December 11, 1983; age 74. Dr

Holz was a 1937 graduate of the New York University College of Medicine. He was a member of the Academy of Medicine, the Nassau County Medical Society, and the Medical Society of the State of New York.

Edward E. Jemerin, MD, New York. Died December 3, 1983; age 75. He was a 1932 alumnus of the New York University College of Medicine, a Fellow of the American College of Surgeons, and a Diplomate of the American Board of Surgery. His memberships included the Academy of Medicine, the New York State Surgical Society, the American Geriatrics Society, the New York County Medical Society, and the Medical Society of the State of New York.

Irving R. Juster, MD, Glens Falls. Died November 18, 1983; age 84. He was a 1922 graduate of the Columbia University College of Physicians and Surgeons. Dr Juster was a Fellow of the American College of Cardiology and a Fellow of the American College of Physicians. His memberships included the Medical Society of the County of Warren and the Medical Society of the State of New York.

Reuben Lavine, MD, Syracuse. Died November 16, 1983; age 87. Dr Lavine was a 1919 alumnus of the State University of New York Upstate Medical Center. He was a member of the Onondaga County Medical Society and the Medical Society of the State of New York.

Ida Mayer, MD, New York. Died November 7, 1983; age 80. Dr Mayer was a 1930 graduate of Johann-Wolfgang-Goethe-University Medical Fakultat, Frankfurt-Am-Main, Prussia. She was a member of the New York County Medical Society and the Medical Society of the State of New York.

Robert J. McCaffrey, MD, Hilton. Died July 13, 1983; age 55. Dr McCaffrey was a 1967 graduate of the University of Maryland School of Medicine. He was a member of the Medical Society of the County of Monroe and the Medical Society of the State of New York.

John Augustus O'Brien, MD, Warwick. Died November 26, 1983; age 40. Dr O'Brien was a 1972 alumnus of the Universidad Autonoma Facultad de Medicina, Guadalajara. He was a Diplomate of the American Board of Pediatrics, and a member of the American Academy of Pediatrics, the Medical Society of the County of Orange, and the Medical Society of the State of New York.

Max Rakofsky, MD, New York. Died November 18, 1983; age 73. He was a 1934 graduate of the Licentiate of the Royal College of Physicians of Edinburgh. Dr Rakofsky was a Fellow of the American College of Chest Physicians, a Diplomate of the American Board of Radiology, a member of the American Thoracic Society, the Society of Nuclear Medicine, the New York County Medical Society, and the Medical Society of the State of New York.

William Rechter, MD, New York. Died October 13, 1983; age 77. Dr Rechter was a 1935 graduate of Deutsche Universitat Medizinische Fakultat, Prague. He was a member of the New York County Medical Society and the Medical Society of the State of New York.

Henry Arthur Rusch, MD, New York. Died October 14, 1983; age 78. He was a 1934 graduate of Columbia University College of Physicians and Surgeons. Dr Rusch was a member of the Academy of Medicine, the American Academy of Allergy, the New York County Medical Society and the Medical Society of the State of New York.

John Boynton Scott, MD, Newburgh. Died November 28, 1983; age 73. He was a 1937 graduate of McGill University Faculty of Medicine. Dr Scott was a member of the American Academy of Family Practice, the Medical Society of the County of Orange, and the Medical Society of the State of New York.

Arthur I. Stecker, MD, Larchmont. Died November 18, 1983; age 71. Dr Stecker was a 1950 graduate of the Ohio State University College of Medicine. He was a member of the Clinical Society, New York Diabetes Association, the New York County Medical Society, and the Medical Society of the State of New York.

Sydney Stonehill, MD, Rochester. Died November 11, 1983; age 69. He was a 1939 graduate of the State University of Iowa College of Medicine. Dr Stonehill was a Fellow of the American College of Physicians, a Fellow of the American College of Chest Physicians, and a Diplomate of the American Board of Internal Medicine. His memberships included the Medical Society of the County of Monroe and the Medical Society of the State of New York.

Herman Tannenbaum, MD, New York. Died December 18, 1983; age 78. He was a 1929 graduate of Cornell University Medical College. Dr Tannenbaum was a Diplomate of the American Board of Family Practice, a Fellow of the American Academy of Family Practice, and a member of the Academy of Medicine, the New York County Medical Society, and the Medical Society of the State of New York.

Louis A. Trippe, MD, Buffalo. Died November 22, 1983; age 70. Dr Trippe was a 1940 graduate of the University of Buffalo School of Medicine. He was a Fellow of the American College of Obstetricians and Gynecologists and a Diplomate of the American Board of Obstetrics and Gynecology. His memberships included the Medical Society of the County of Erie and the Medical Society of the State of New York.

Gloria D. Marmar Warner, MD, New York. Died November 30, 1983; age 50. Dr Warner was a 1959 alumnus of New York University College of Medicine. A Diplomate of the American Board of Psychiatry and Neurology, her memberships included the American Psychiatric Association, the American Medical Women's Association, the American Psychoanalytic Association, the Academy of Psychoanalysis, the New York County Medical Society, and the Medical Society of the State of New York.

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The *New York State Journal of Medicine* welcomes research papers and original essays on the practice of medicine, medical education, public health, the history of medicine, medicolegal matters, legislation, ethics, the mass media and socioeconomic issues in health care.

Manuscripts should be prepared according to the "Uniform requirements for manuscripts submitted to biomedical journals" (*NY State J Med* 1983; 83:1089–1094). The requirements were established by the International Committee of Medical Journal Editors, of which the *Journal* is a participating member. These Guidelines are intended to highlight aspects of the *Journal*'s particular style of publication.

A manuscript will be considered for publication if it is original, has not been published previously in whole or in part in either a medical journal or a lay publication, and is not simultaneously under consideration elsewhere. A copy of any possibly duplicative material, such as a reference "in press," should be submitted along with the manuscript.

PREPARATION

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A corresponding author should be designated in the covering letter. Authors should list their title and affiliation at the time they did the work, and, if different, their present affiliation. The addresses and telephone numbers of all authors should be supplied for editorial purposes. All authors of a manuscript are responsible for having read and approved it for submission.

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Research Papers should be limited to 2,500 words and should include the following sections: Introduction, Methods, Results, Discussion, and References. Multiple subheadings and numbered lists are discouraged. An abstract limited to 150 words should state the reasons for the study, the main findings, and their implications. Statistical evaluations should be described in the Methods section, and the name and affiliation of the statistician should be included in the acknowledgments if this individual is not listed as a coauthor. Reports of experiments involving human subjects must include a description in the Methods section of the informed consent obtained and a statement that the procedures followed were approved by an institutional research review committee. Anonymity of patients must be preserved. Reports of experiments on animals must note which guidelines were followed for the care and use of laboratory animals.

Case Reports should be limited to 1,250 words. Review Articles should not exceed 3,000 words. Commentaries should be between 750 and 1,000 words. Other kinds of original essays should not exceed 2,000 words. A letter of inquiry should be sent to the editor prior to submitting a Review Article or Commentary.

For Research Papers only, scientific measurements should be given in conventional units, with Système Internationale (SI) units in parentheses. Abbreviations and acronyms should be kept to a minimum, and jargon should be avoided. Generic names of drugs should be used instead of brand names.

FIGURES

The submission of color illustrations or slides is discouraged. Only black and white glossy photographic prints or "camera-ready" artwork will be accepted. The *Journal* is unable to provide art services such as the addition of arrows to photographs. A signed consent for publication must accompany photographs in which the patient is identifiable. Illustrations from other publications generally will not be considered. Legends for illustrations should be typed on a separate sheet, and for photomicrographs should include magnification and stain. Each illustration should be lightly marked on the back in pencil with the name of the first author, the number as cited in the text, and an arrow indicating the top. Each set of illustrations should be submitted unmounted in a separate envelope.

Tables should be simple, self-explanatory, and few in number. Each table should be typed double-spaced on a separate sheet.

REFERENCES

References should be limited to the most pertinent. The recommended maximum number of references is 25 for Research Papers and most other original contributions (except lengthier Review Articles), 12 for Commentaries and Case Reports, and six for letters to the editor.

Authors are responsible for the accurate citation of references. Citation of secondary sources is discouraged except where the original reference is unobtainable. Authors may not cite references they have not read, and the use of abstracts as references should be avoided.

References should be indicated in the text by superscript numbers following the name of the author (eg, Smith^2 reported two cases).

The list of references at the end of the article should be typed double-spaced and references should be numbered in the order in which they appear on the text. When there are six or fewer authors, all should be listed; where there are seven or more, the first three should be listed, followed by *et al.* Names of journals should be abbreviated according to *Index Medicus* and underlined.

Sample references:

1. Kepes ER, Thomas P, Vemulapalli K: Methadone and intravenous morphine requirements. *NY State J Med* 1983; 83:925–927.
2. McGuigan JE. Peptic ulcer. In: Petersdorf RG, Adams RD, Braunwald E, Isselbacher KJ, Martin JB, Wilson JD, eds. *Harrison's Principles of Internal Medicine*. New York, McGraw-Hill, 1983, pp 1697–1712.

REVIEW

All manuscripts are reviewed by the editors, and most manuscripts are sent to outside referees. Decisions concerning acceptance, revision, or rejection of a manuscript are usually made within three to six weeks. Every effort will be made to assure prompt publication of an accepted manuscript. A galley proof will be sent to the author for approval prior to publication.

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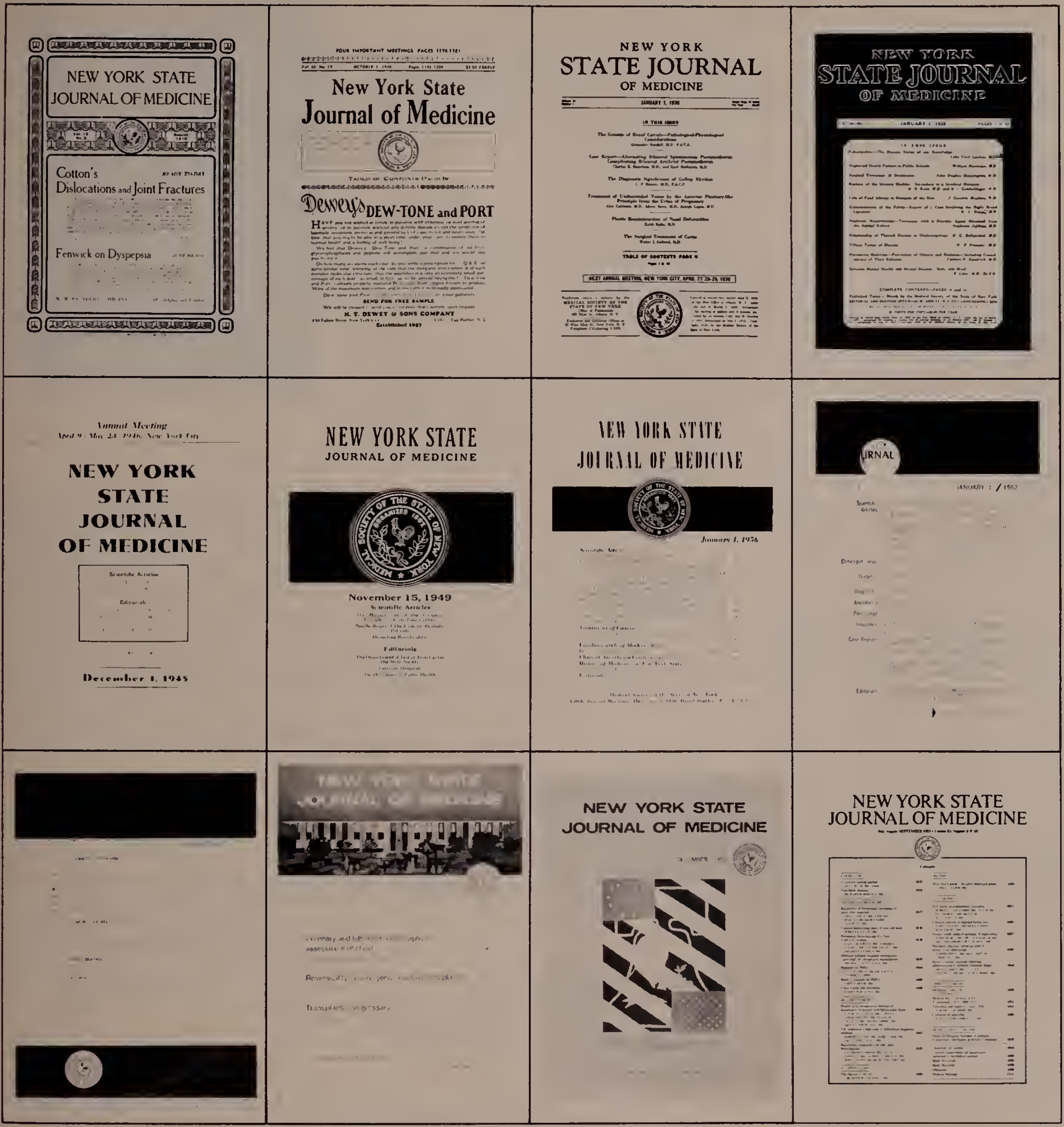

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June 4-6. **Third Annual Obstetrical Ultrasound.** 19 Cat 1 credits. Info: Registration Office, NYU Post-Graduate Medical School, 550 First Avenue, New York, NY 10016. Tel: (212) 340-5295.

June 6. **Trainees' Night, Section on Pediatrics with the New York Pediatric Society and Chapters 2 and 3 of District II of the American Academy of Pediatrics.** Info: The New York Academy of Medicine Programs, 2 E 103 St, New York, NY 10029. Tel: (212) 876-8200.

June 6-9. **International Conference on Disability Compensation for Occupational Disease.** Info: NYS Workers' Compensation Board, Office of Communication Information and Education, Room 4099, 2 World Trade Center, New York, NY 10047. Tel: (212) 488-3100.

June 10-11. **Phenylpropanolamine: Benefits and Risks.** Info: Doreen Kagan, Conference Administrator, Sophie Davis School of Biomedical Education, Rm J903, The City College of The City University of New York, New York, NY 10031.

June 11-15. **Update Your Medicine 1984.** Info: Dr Lila Wallis, Office of CME, New York Hospital-Cornell, 1300 York Avenue at 69th Street, New York, NY 10021. Tel: (212) 472-6119 or 5600.

June 11-15. **Emergency Medicine 1984. A Two Track Course: Medicine/Surgery.** 29 Cat 1 credits. Info: Registration Office, New York University Post-Graduate Medical School, 550 First Ave, New York, NY 10016. Tel: (212) 340-5295.

June 13-15. **Surgical Courses in Lens Implantation.** Info: Ruth Green, Administrator, Ophthalmological Foundation of America, 823 United Nations Plaza, New York, NY 10017. Tel: (212) 986-4848.

June 21. **Sleep Disorders.** 2 Cat 1 credits. Info: Diane Du-Prey, Medical Staff Secretary, Union Hospital of the Bronx, 260 E 188th St, Bronx, NY 10458. Tel: (212) 220-2020.

June 22. **Clinical Urodynamics: A Practical Approach.** 7 Cat 1 credits. Info: Kathy R. Bonomo, Beth Israel Medical Center, 10 Nathan D. Perlman Place, New York, NY 10003. Tel: (212) 420-2000.

BRONX

June 7. **Clinical Grand Rounds: "Approach to the Chest."** *June 21.* **"Diabetes Melittus."** 2 Cat 1 credits. Info: Dr Frank Quattromani, Director, CME Program, Westchester Square Medical Center, 2475 St Raymond Ave, Bronx, NY 10461.

BROOKLYN

June 1. **Narcotics in Anesthesia—Old and New—A Symposium.** 6 Cat 1 credits. Info: Kurt G. Becker, Exec Director, The New York State Society of Anesthesiologists. 30 E 42 St, Suite 1501, New York, NY 10017. Tel: (212) 867-7140.

June 3. **Clinical Diabetes.** Info: Hazel Spadafora, Exec Director, Kings County Medical Society, 1313 Bedford Ave, Brooklyn, NY 11216. Tel: (212) 467-9000.

June 6. **Syncope—To Admit or Not to Admit.** 2 Cat 1 credits. Info: Ingrid Schmidt, Center for Continuing Education, Kings County Health Care Review Organization, Inc., 1313 Bedford Ave., Brooklyn, NY 11216. Tel: (212) 467-9032, ext. 36.

June 19. **Recognition and Management of Seleced Cardiac Problems in the Geriatric Patient.** Info: Morris Kleinfeld, MD, Director Chairman, Medical Education Committee, Kingsbrook Jewish Medical Center, Rutland Rd and E 49 St, Brooklyn, NY 11203. Tel: (212) 756-9700.

QUEENS

June 1. **The Rational Use of Aerosol Broncho Dilators.** *June 4.* **Gastrointestinal Manifestations of Immuno Deficiencies Syndrome.** *June 5.* **Sub-cortical Dementia.** *June 7.* **Prognostic Implication on Non-transmural vs Transmural Infarctions.** *June 11.* **Recent Advances in Obstetrics & Gynecology.** *June 12.* **Collagen Vascular Disorders-Renal Manifestations.** *June 13.* **Evaluation of a Patient with Heart Murmur.** *June 15.* **Infectious Diseases of Lung.** *June 22.* **Shock and Electrolytes and Fluid Management.** Info: Postgraduate Educational Programs, The Jamaica Hospital Medical Center, 89th Ave & Van Wyck Expressway, Jamaica, NY 11418. Tel: (212) 657-1800.

June 5. **Pathophysiology and Treatment of Heart Failure.** *June 12.* **Pathophysiology and Treatment of Respiratory Failure.** *June 19.* **Pathophysiology and Treatment of Chronic Renal Failure.** *June 26.* **Multiple Organ Failure.** 1½ Cat 1 credits. Info: Luisa P. Gonzalez, Coordinator, CME, Flushing Hospital and Medical Center, 4500 Parsons Blvd, Flushing, NY 11355-9980. Tel: (212) 670-5741.

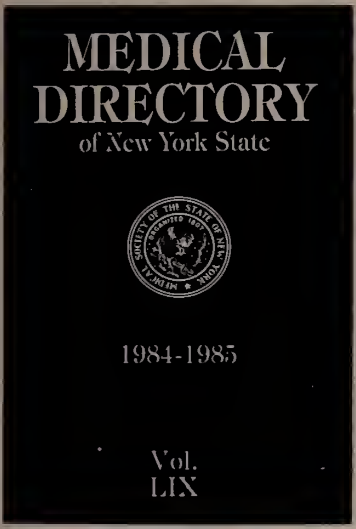
NASSAU

June 7-9. **1st Annual Long Island Assembly of Obstetrics & Gynecology "Current Concepts—1984."** 19 Cat 1 credits. Info: Ann J. Boehme, Continuing Education Coordinator, Long Island Jewish-Hillside Medical Center, New Hyde Park, NY 10042. Tel: (212) 470-2114.

SUFFOLK

June 5. **Outcome of Neonatal Intensive Care.** *June 12.* **The Pedicatrician as a Hematologist.** Info: Arthur Schwager, MD, Chairman, Pediatric CME, Huntington Hospital, 270 Park Ave, Huntington, NY 11743. Tel: (516) 427-0530.

June 20-23. **Questions in Emergency Medicine.** 24 Cat 1 credits. Info: Tamareth K. Yolles, MD, Associate Dean for CME, School of Medicine (HSC) L4/Rm 178, SUNY-Stony Brook, Stony Brook, NY 11794-8437. Tel: (516) 444-2094.



ANNOUNCING THE
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The Directory lists over 25,000 New York State physicians, both members of the Medical Society, and non-members who chose to be listed for a fee. It includes the following data:

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★**O'CONNOR, Robert James,** 33 Valencia Ave 10301. Tel 447-7242. STATE UNIV BKLN 51. D-OG. SL. FACOG. FICS. Am Abdominal Sur. Am Ac Comp Med. Attd O&G Staten Isl. Cons O&G USPHSH SI. Attd Gyn Sea View. Also Lake Success (MEM-AMA)

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BUFFALO

June 7. **Prevention of Cancer.** Info: Gayle Bersoni, RN, Cancer Control Coordinator, Roswell Park Memorial Institute, 666 Elm St, Buffalo, NY 14263. Tel: (716) 845-4406.

June 9. **Asthma and Other Allergic Diseases, Management by Primary Care Physicians.** 6 Cat 1 credits. Info: Rayna Dutton, CME Coordinator, Dept of Pediatrics, SUNY-Buffalo, 219 Bryant St, Buffalo, NY 14222. Tel: (716) 878-7630.

June 11-13. **Update on Anesthesia and the Heart.** 4 Cat 1 credits. Info: Kurt G. Becker, Exec Director, The New York State Society of Anesthesiologists. 30 E 42 St, Suite 1501, New York, NY 10017. Tel: (212) 867-7140.

June 25-28. **International Convocation on Immunology. Antibodies: Protective, Destructive and Regulatory Role.** Info: Dr James F. Mohn, Director, The Ernest Witebsky Center for Immunology, 210 Sherman Hall, SUNY-Buffalo, Buffalo, NY 14214. Tel: (716) 831-2848.

SYRACUSE

June 1-2. **Interventions and Rehabilitation in Aging.** 9 Cat 1 credits. *June 6.* **Post-Graduate Education Day. Pediatrics "Conversations with Melvin D. Levine and John D. Nelson."** 7 Cat 1 credits. Info: Office of Continuing Education, SUNY Upstate Medical Center, 766 Irving Avenue, Syracuse, NY 13210. Tel: (315) 473-4606.

AROUND THE NATION

ALASKA

June 9-11. **Alaska Academy of Family Physicians, annual meeting.** Valdez. Info: Dr Jon Koivuhen, AAFP, Box 1760, Wasilla, AL 99687.

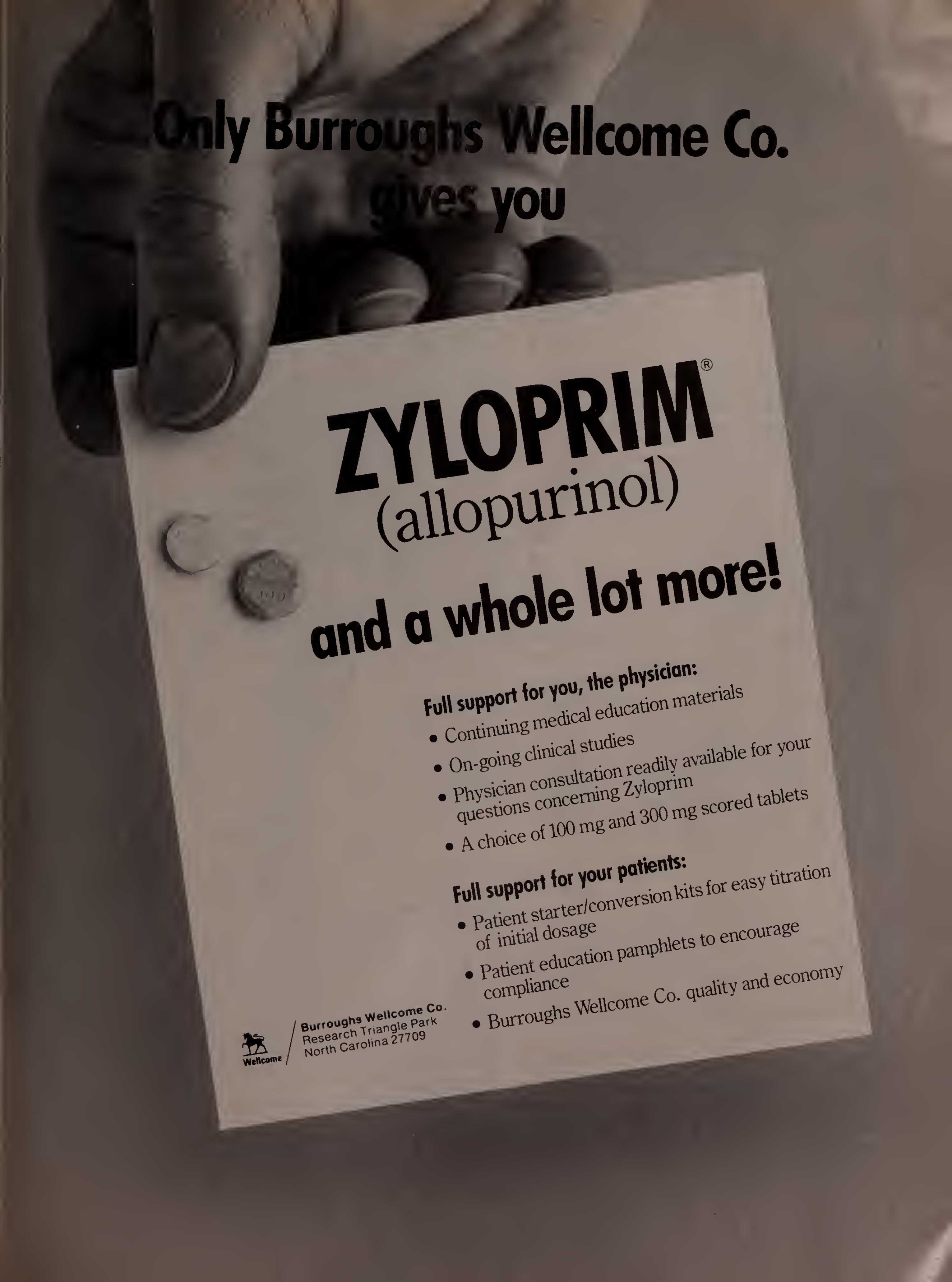
CALIFORNIA

June 14-16. **American Cancer Society National Conference on Radiation Oncology.** 16 Cat 1 credits. Info: American Cancer Society, National Conference on Radiation Oncology, 777 Third Ave, New York, NY 10017. Tel: (212) 371-2900.

June 14-18. **Management of Pain #8.** San Francisco. 31 Cat 1 credits. Info: Conference Coordinator, Academy of Pain Research, 1515 Sloat Blvd, Suite 5, San Francisco, CA 94132. Tel: (415) 731-1330.

June 17-19. **14th Annual Symposium on Chest Disease.** 22 Cat 1 credits. Info: The Fleischner Society, Naomi Feldman, 3770 Tansy St, San Diego, CA 92121. Tel: (619) 453-6222.

June 17-23. **UCI Family Practice Refresher Course.** Anaheim. Info: Assistant Director, Center for Health Education, 2801 Atlantic Ave, Long Beach, CA 90801-1428.



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Navy Medical Programs
Federal Building
111 West Huron Street
Buffalo, New York 14202
1-800-822-8838

COLORADO

June 14–15. **Ethics, Values and Rights. An interdisciplinary conference on practical approaches to dealing with ethical issues in the hospital setting.** Denver. Info: American Hospital Association, PO Box 98946, Chicago, IL 60693. Tel: (312) 280–6083.

DELAWARE

June 17–22. **Eastern Shore Medical Symposium.** Rehoboth Beach. Info: Sylvia Brocka, University of Delaware, Division of Continuing Education, 2800 Pennsylvania Ave, Wilmington, DE 19806. Tel: (302) 451–8151.

FLORIDA

June 8–10. **Providing Quality Medical Care in Your Practice.** Ponte Vedra Beach. Info: Jeanette Stone, Southern Medical Association, PO Box 2446, Birmingham, AL 35201. Tel: (205) 323–4400.

ILLINOIS

May 29–June 9. **Specialty Review in Family Practice.** Chicago. 91 Cat 1 credits. Info: The Cook County Graduate School of Medicine, 707 S Wood St, Chicago, IL 60612. Tel: (800) 621–4651.

KANSAS

June 7–9. **Kansas Academy of Family Physicians, annual meeting.** Lawrence. Info: Gene M Wilcox, Exec Secretary, Kansas Academy of Family Physicians, 404 State Bank Bldg, Winfield, KA 67156.

LOUISIANA

June 10–12. **Family Medicine Update.** New Orleans. Info: V. Jean Taylor, Conference Coordinator, Continuing Medical Education, University of Tennessee, Center for Health Sciences, 800 Madison Ave, Memphis 38163.

MARYLAND

June 1–2. **Topics in Cardiovascular Diseases: Cardiac Arrhythmias.** Baltimore. Info: Michaeline R. Silverstein, Deputy Exec Director, American Heart Assoc, 415 N Charles St, PO Box 17025, Baltimore, MD 21203. Tel: (301) 685–7074.

June 7–8. **Potassium in Cardiovascular and Renal Medicine.** Baltimore. 14 Cat 1 credits. Info: Diane Heydinger, The Johns Hopkins University School of Medicine, Office of Continuing Education, Turner 22, 720 Rutland Ave, Baltimore, MD 21205. Tel: (301) 955–6046.

June 17–22. **Annual Family Medicine Review Course, PG.** Ocean City. Info: Office of Continuing Education, University of Maryland, School of Medicine, Medical School Teaching Facility, 10 S Pine St, Room 300, Baltimore, MD 21201.

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FAMILY PRACTICE PHYSICIAN, Board certified, seeks practice opportunity in NYC area, specialty interests in preventive medicine, sports medicine, teaching. Ben Thomas, M.D., Box 685 Oakridge Apts., Oakwood, Georgia 30566.

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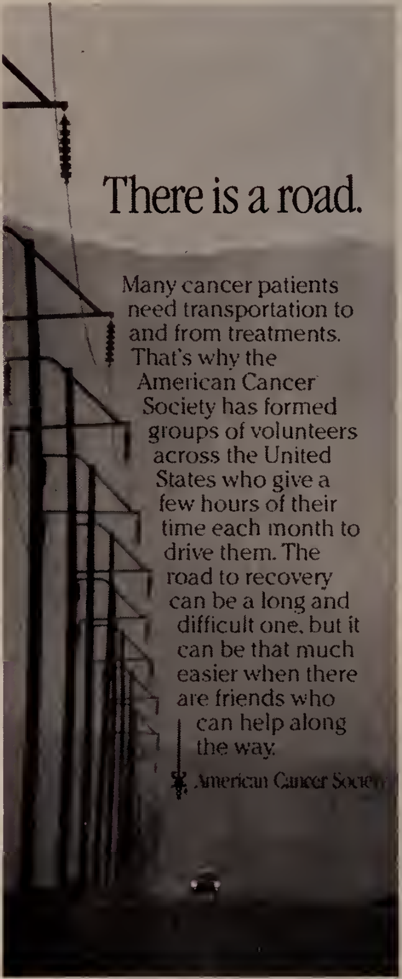

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MASSACHUSETTS

June 1–2. **Contact and Panoramic Hysteroscopy.** Boston. 14 Cat 1 credits. *June 21–22.* **Female Urinary Incontinence.** Boston. 16 Cat 1 credits. Info: Harvard Medical School, Dept of Continuing Education, Boston, MA 02115. Tel: (617) 732-1525.

June 1–3. **Family Medicine Update, PG.** Cape Cod. Info: Office of Continuing Education, University of Massachusetts Medical School, 55 Lake Ave N, Worcester, MA 01605.

June 25–August 31. **Cape Code Summer Symposia.** Psychiatry. Cape Cod. Info: New England Educational Institute, Dept of Continuing Education, PO Box 715, Lenox, MA 01240. Tel: (413) 637-0101.

MISSOURI

June 7–10. **Missouri Academy of Family Physicians, annual scientific assembly.** Lake Ozark. Info: Roxy Van Gallera, Missouri Academy of Family Physicians, 2920 McGee Trafficway, Kansas City, MO 64108.

PENNSYLVANIA

June 20–24. **Pennsylvania Academy of Family Physicians, annual convention and scientific assembly.** Bedford. Info: Calder C. Murlott, Jr, PAFP, 5600 Derry St, Harrisburg, PA 17111.

June 21–24. **1984 Annual Pennsylvania Allergy Association Conference.** Hershey. Info: Walter F. Fullam, 500 University Dr, Hershey, PA 17033. Tel: (717) 534-6489.

TENNESSEE

June 14–15. **Malpractice Prophylaxis.** Memphis. Info: Jeanette Stone, Southern Medical Assoc, PO Box 2446, Birmingham, AL. Tel: (205) 323-4400.

TEXAS

June 16–17. **Plastic Surgery Educational Foundation—Instructional Course Symposium.** 16 Cat 1 credits. Houston. Info: PSEF, 233 North Michigan Ave, Suite 1900, Chicago, IL 60601. Tel: (312) 856-1818.

VERMONT

June 17–21. **Family Practice Review Course, PG.** Sugarbush. Info: Maureen Hanagan, Coordinator, Office of Continuing Medical Education, University of Vermont College of Medicine, Burlington, VT 05405.

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VIRGINIA

May 29–June 1. **Eighth Annual Flap Dissection Workshop.** 33.5 Cat 1 credits. Norfolk. Info: Vicky Martin, Hague Medical Center, Suite 300, 400 W Brambleton Ave, Norfolk, VA 23516. Tel: (804) 623-1090.

June 18–20. **Symposium on Tumor Promotion and Enhancement in the Etiology of Human and Experimental Respiratory Tract Carcinogenesis.** Williamsburg. Info: Dave Tisch and Catherine Bollinger, Northrop Services, Inc. PO Box 12313, Research Triangle Park, NC 27709. Tel: (919) 549-0652.

June 21–23. **Medical and Surgical Management of Common Orthopedic and Connective Tissue Disorders, PG.** Virginia Beach. Info: Randy Casey, Program Coordinator. Office of Continuing Medical Education, School of Medicine, Box 48, MCV Station, Richmond, VA 23298.

June 21–23. **Bones, Joints, and Sports Medicine for the Non-Orthopedic Physician.** Virginia Beach. 12 Cat 1 credits. Info: Mrs Kay Parrott, Box 48, MCV Station, Richmond, VA 23298.

WASHINGTON, DC

June 8–10. **Sixth Annual Institute on Medical Hypnosis.** 20 Cat 1 credits. Info: Office of Continuing Medical Education, The George Washington University Medical Center, 2300 K St NW, Washington, DC 20037. Tel: (202) 676-4285.

References:
1. Stone PH, Turi ZG, Muller JE: Efficacy of nifedipine therapy for refractory angina pectoris. *Am Heart J* 104:672-681, September 1982.
2. Antman E, Muller J, Goldberg S, et al: Nifedipine therapy for coronary-artery spasm: Experience in 127 patients. *N Engl J Med* 302:1269-1273, June 5, 1980.

BRIEF SUMMARY
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II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in those patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See Warnings.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving PROCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PROCARDIA and a beta blocker, but the possibility that it may occur with PROCARDIA alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In PROCARDIA treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for PROCARDIA to be washed out of the body prior to surgery.

Increased Angina: Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Beta Blocker Withdrawal: Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients, usually receiving a beta blocker, have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See Warnings.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Drug Interactions: Beta-adrenergic blocking agents: (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing PROCARDIA to avoid possible over- or under-digitalization.

Carcinogenesis, mutagenesis, impairment of fertility: When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose.

Pregnancy: Category C. Please see full prescribing information with reference to teratogenicity in rats, embryotoxicity in rats, mice and rabbits, and abnormalities in monkeys.

ADVERSE REACTIONS: The most common adverse events include dizziness or light-headedness, peripheral edema, nausea, weakness, headache and flushing each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Additionally, the following have been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, diarrhea, constipation, inflammation, joint stiffness, shakiness, sleep disturbances, blurred vision, difficulties in balance, dermatitis, pruritus, urticaria, fever, sweating, chills, and sexual difficulties. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

Laboratory Tests: Rare, mild to moderate, transient elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted, and a single incident of significantly elevated transaminases and alkaline phosphatase was seen in a patient with a history of gall bladder disease after about eleven months of nifedipine therapy. The relationship to PROCARDIA therapy is uncertain. These laboratory abnormalities have rarely been associated with clinical symptoms. Cholestasis, possibly due to PROCARDIA therapy, has been reported twice in the extensive world literature.

HOW SUPPLIED: Each orange, soft gelatin PROCARDIA CAPSULE contains 10 mg of nifedipine. PROCARDIA CAPSULES are supplied in bottles of 100 (NDC 0069-2600-66), 300 (NDC 0069-2600-72), and unit dose (10x10) (NDC 0069-2600-41). The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

More detailed professional information available on request. © 1982, Pfizer Inc

Pfizer **LABORATORIES DIVISION**
PFIZER INC

"I can do things that I couldn't do for 3 yrs. including joining the human race again."

Quotes from an unsolicited letter received by Pfizer from an angina patient
While this patient's experience is representative of many unsolicited comments received not all patients will respond to Procardia nor will they all respond to the same degree.

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"My daily routine consisted of sitting in my chair trying to stay alive."

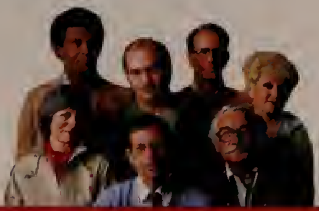
"My doctor switched me to PROCARDIA[*] *as soon as it became available. The change in my condition is remarkable."*

"I shop, cook and can plant flowers again."

"I have been able to do volunteer work...and feel needed and useful once again."

PROCARDIA can mean the return to a more normal life for your patients—having fewer anginal attacks,[1] taking fewer nitroglycerin tablets,[2] doing more, and being more productive once again.

Side effects are usually mild (most frequently reported are dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%).



for the varied faces of angina

PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

Please see PROCARDIA *brief summary on adjoining page.*

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* Procardia is indicated for the management of:
1) Confirmed vasospastic angina.
2) Angina where the clinical presentation suggests a possible vasospastic component.
3) Chronic stable angina without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or nitrates or who cannot tolerate these agents. In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks' duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

MISCELLANEOUS—CONT'D

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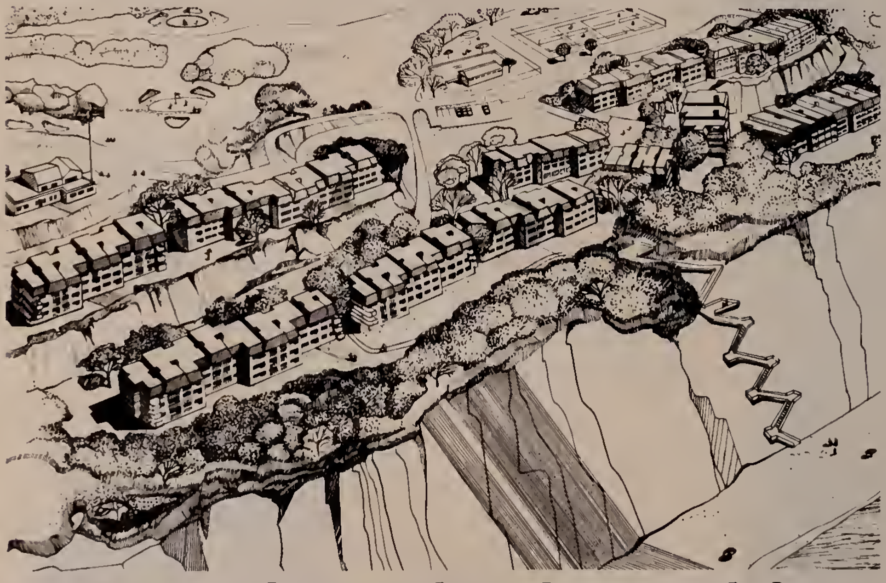

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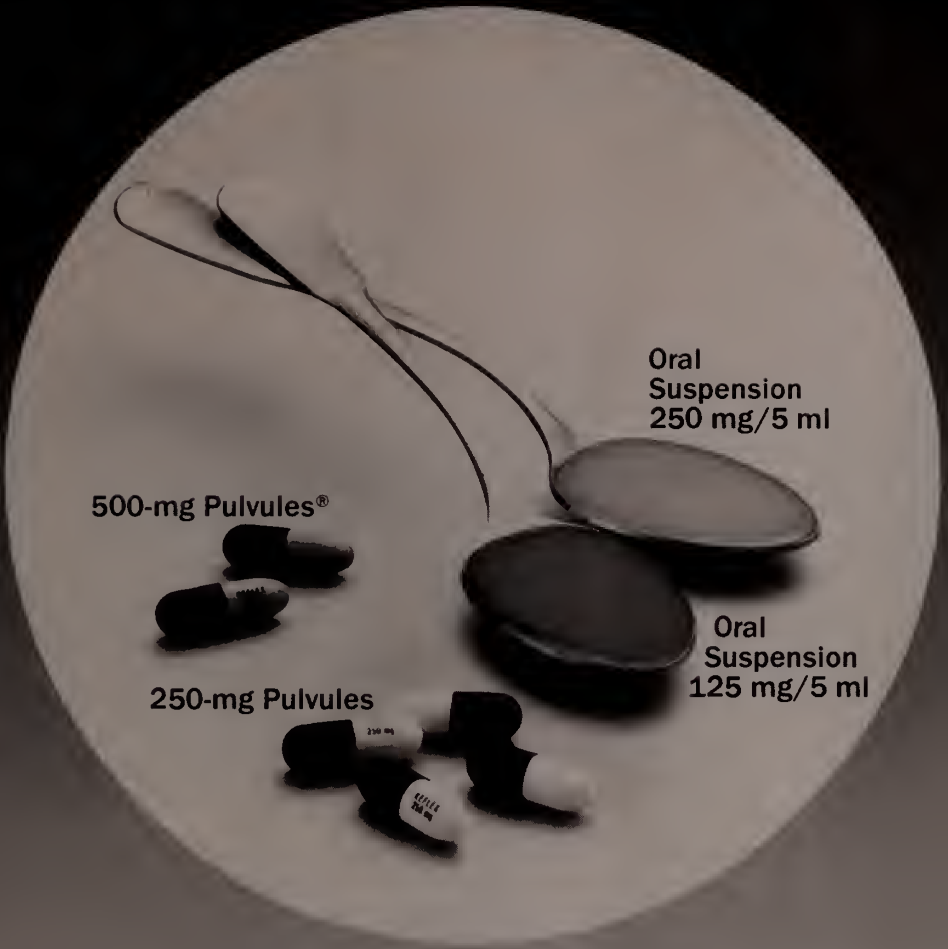

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Just once each day...

First-step blood pressure control with optimal simplicity

Benefits diuretics cannot offer . . . Once-daily INDERAL LA (propranolol HCl) provides smooth, 24-hour control of blood pressure plus the cardiovascular benefits of the world's leading beta blocker. And INDERAL LA provides a high degree of patient acceptance—without potassium problems.

Experience no other beta blocker can match . . . Once-daily INDERAL LA delivers the proven performance and safety profile of INDERAL tablets—confirmed by millions of patients during 16 years of clinical use. INDERAL LA should not be used in congestive heart failure, sinus bradycardia, heart block greater than first degree, or bronchial asthma.

Start with 80 mg once daily... Dosage may be increased to 120 mg or 160 mg once daily as needed to achieve additional control. Please see next page for further details and brief summary of prescribing information.

ONCE-DAILY

INDERAL LA

(PROPRANOLOL HCl) LONG-ACTING CAPSULES

Just once each day for initial therapy in hypertension.

80 mg 120 mg 160 mg

Ayerst

Just once each day for initial therapy in HYPERTENSION.

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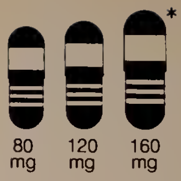
INDERAL® LA

(PROPRANOLOL HCl) LONG ACTING CAPSULES



BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)*
INDERAL® LA brand of propranolol hydrochloride **(Long Acting Capsules)**

DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.

CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period

The mechanism of the antihypertensive effect of INDERAL has not been established Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients

In angina pectoris, propranolol generally reduces the oxygen re[illegible]t any given level of effort by blocking the catecholamine-[illegible] inc[illegible] in the heart rate, systolic blood pressure, and the velocity and extent of myocardial [illegible]nolol may increase oxygen requirements by increasing left ventricular fiber length, [illegible]stolic pressure and systolic ejection period The net phy[illegible] adrener[illegible]de is usually advantageous and is manifested during exercise [illegible] of [illegible]nd increased work capacity

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects th[illegible]c a[illegible]nti[illegible]ig cance of the membrane action in the treatment of arrhythmias is uncer[illegible]

The mechanism of the antimigraine effect of propranolol [illegible]lished B[illegible] adrenergic receptors have been demonstrated in the pial vessels of the [illegible]

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrim[illegible]u[illegible]so situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension, it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL

WARNINGS. CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible)

> IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. It INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors

MAJOR SURGERY. The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers

DIABETES AND HYPOGLYCEMIA Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS. Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. *General:* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure

Clinical Laboratory Tests Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential In 18-month studies in [illegible] rats [illegible] empl[illegible] doses [illegible] 150 mg/kg/day, there was no evidence of significant [illegible]lated tumorigenic effects at any of the dosage level[illegible] duc[illegible]dies [illegible]als [illegible] not show any impairment of fertility that was attri[illegible] to th[illegible]

[illegible]ncy: [illegible]ncy Cat[illegible]ry C. INDERAL has been shown to be embryotoxic in [illegible]ies a[illegible]er than the maximum recommended human dose

There are no adequate and well-controlled studies in pregnant women INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Nursing Mothers: INDERAL is excreted in human milk Caution should be exercised when INDERAL is administered to a nursing woman.

Pe[illegible] [illegible]ely a[illegible]ctiveness in children have not been established

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block, hypotension; [illegible] thr[illegible] purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics

Just once each day...

Gastrointestinal. nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported

Miscellaneous. alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily It patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained INDERAL LA should not be considered a simple mg for mg substitute for INDERAL INDERAL LA has different kinetics and produces lower blood levels Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval

HYPERTENSION—*Dosage must be individualized* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved The usual maintenance dosage is 120 to 160 mg once daily In some instances a dosage of 640 mg may be required The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established

It treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS)

MIGRAINE—*Dosage must be individualized* The initial oral dose is 80 mg INDERAL LA once daily The usual effective dose range is 160-240 mg once daily The dosage may be increased gradually to achieve optimum migraine prophylaxis It a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued It may be advisable to withdraw the drug gradually over a period of several weeks

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use

*The appearance of INDERAL LA capsules is a registered trademark of Ayerst Laboratories

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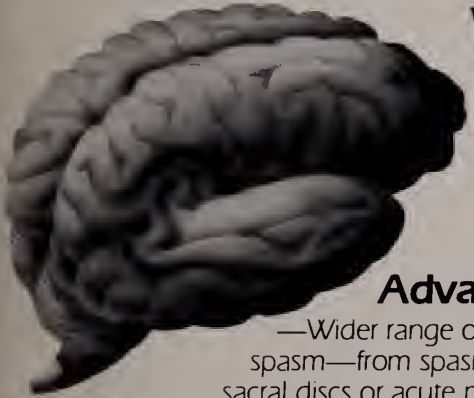
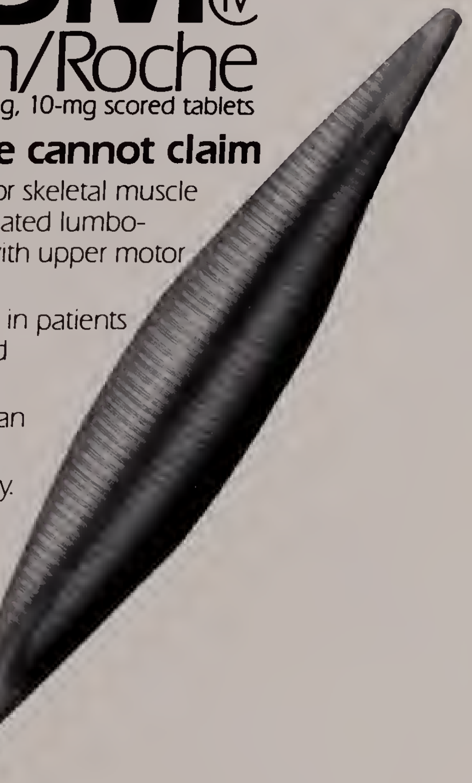
THE SPASM/PAIN/SPASM CYCLE

In skeletal muscle spasm due to local pathology, responsive to the distinct actions of



Adjunctive
VALIUM® Ⓒ
diazepam/Roche
2-mg, 5-mg, 10-mg scored tablets



Advantages cyclobenzaprine cannot claim

—Wider range of indications as adjunctive therapy for skeletal muscle spasm—from spasm due to local pathology (*e.g.*, herniated lumbosacral discs or acute muscle strain) to spasm associated with upper motor neuron disorders (*e.g.*, cerebral palsy and paraplegia).

—May be used adjunctively for relieving skeletal muscle spasm in patients with hyperthyroidism, cardiac patients and patients being treated with anticholinergics or guanethidine-type antihypertensives.

—Can be administered to patients less than 15 years and more than 6 months of age.

—Scored tablets in three strengths provide greater dosage flexibility.

Since drowsiness, fatigue and ataxia sometimes occur, patients should be cautioned against driving or operating hazardous machinery and should also be advised against simultaneous ingestion of alcohol.

References: 1. Rankin EA. *Contin Educ 3*(1):46-50, Jan 1975. **2.** When muscle spasm hobbles your patient. *Patient Care 8*(11):20-37, Jun 1, 1974.

Valium® (diazepam/Roche) Ⓒ
Before prescribing, please consult complete product information, a summary of which follows:
Indications: Management of anxiety disorders, or short-term relief of symptoms of anxiety Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic Symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal, adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not as sole therapy)
The effectiveness of Valium in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies The physician should periodically reassess the usefulness of the drug for the individual patient
Contraindicated: Known hypersensitivity to the drug Children under 6 months of age Acute narrow angle glaucoma, may be used in patients with open angle glaucoma who are receiving appropriate therapy
Warnings: Not of value in psychotic patients Caution against hazardous occupations requiring complete mental alertness When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication, abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures Advise against simultaneous ingestion of alcohol and other CNS depressants Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use, generally at higher therapeutic levels, for at least several months After extended therapy, gradually taper dosage Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence

***Usage in Pregnancy*: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed, drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies Observe usual precautions in impaired renal or hepatic function Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation
The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration The clinical significance of this is unclear
Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported, should these occur, discontinue drug Isolated reports of neutropenia, jaundice, periodic blood counts and liver function tests advisable during long-term therapy
Dosage: Individualize for maximum beneficial effect *Adults* Anxiety disorders, symptoms of anxiety, 2 to 10 mg b.i.d to q.i.d., alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d or q.i.d as needed, adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d or q.i.d., adjunctively in convulsive disorders, 2 to 10 mg b.i.d to q.i.d. *Geriatric or debilitated patients* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated (See Precautions.) *Children*. 1 to 2½ mg t.i.d or q.i.d initially, increasing as needed and tolerated (not for use under 6 months)
How Supplied: For oral administration, round, scored tablets with a cut out "V" design—2 mg, white, 5 mg, yellow, 10 mg, blue— bottles of 100 and 500; Prescription Paks of 50, available in trays of 10. Tel-E-Dose® packages of 100, available in boxes of 4 reverse-numbered cards of 25, and in boxes containing 10 strips of 10

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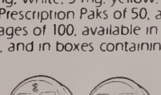

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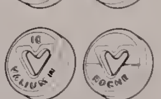

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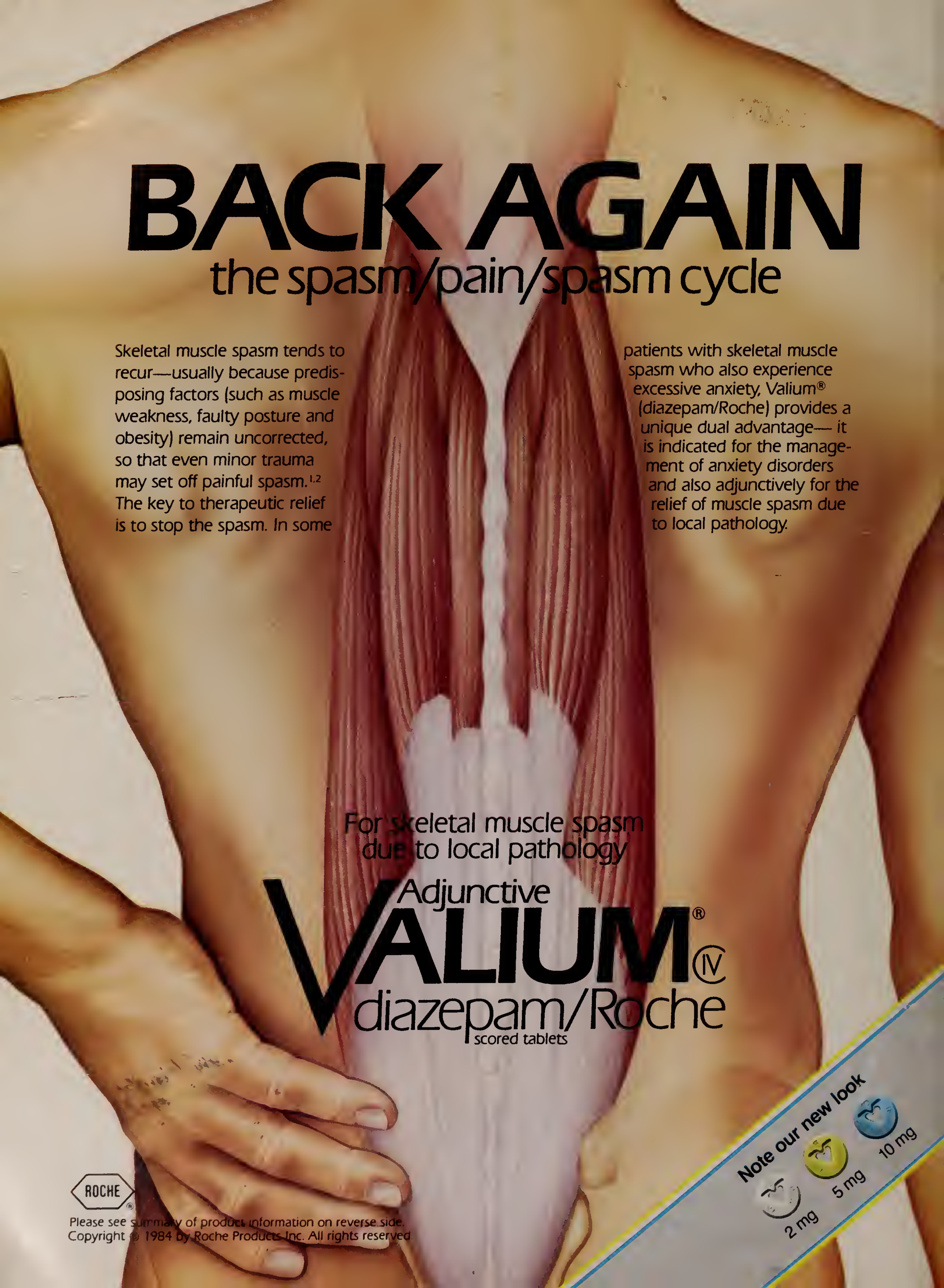

BACK AGAIN
the spasm/pain/spasm cycle

Skeletal muscle spasm tends to recur—usually because predisposing factors (such as muscle weakness, faulty posture and obesity) remain uncorrected, so that even minor trauma may set off painful spasm.[1,2] The key to therapeutic relief is to stop the spasm. In some patients with skeletal muscle spasm who also experience excessive anxiety, Valium® (diazepam/Roche) provides a unique dual advantage— it is indicated for the management of anxiety disorders and also adjunctively for the relief of muscle spasm due to local pathology.

For skeletal muscle spasm due to local pathology

Adjunctive
VALIUM® Ⓘⓥ
diazepam/Roche
scored tablets

ROCHE®

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NEW YORK STATE JOURNAL OF MEDICINE

JUNE 1984 • Volume 84, Number 6

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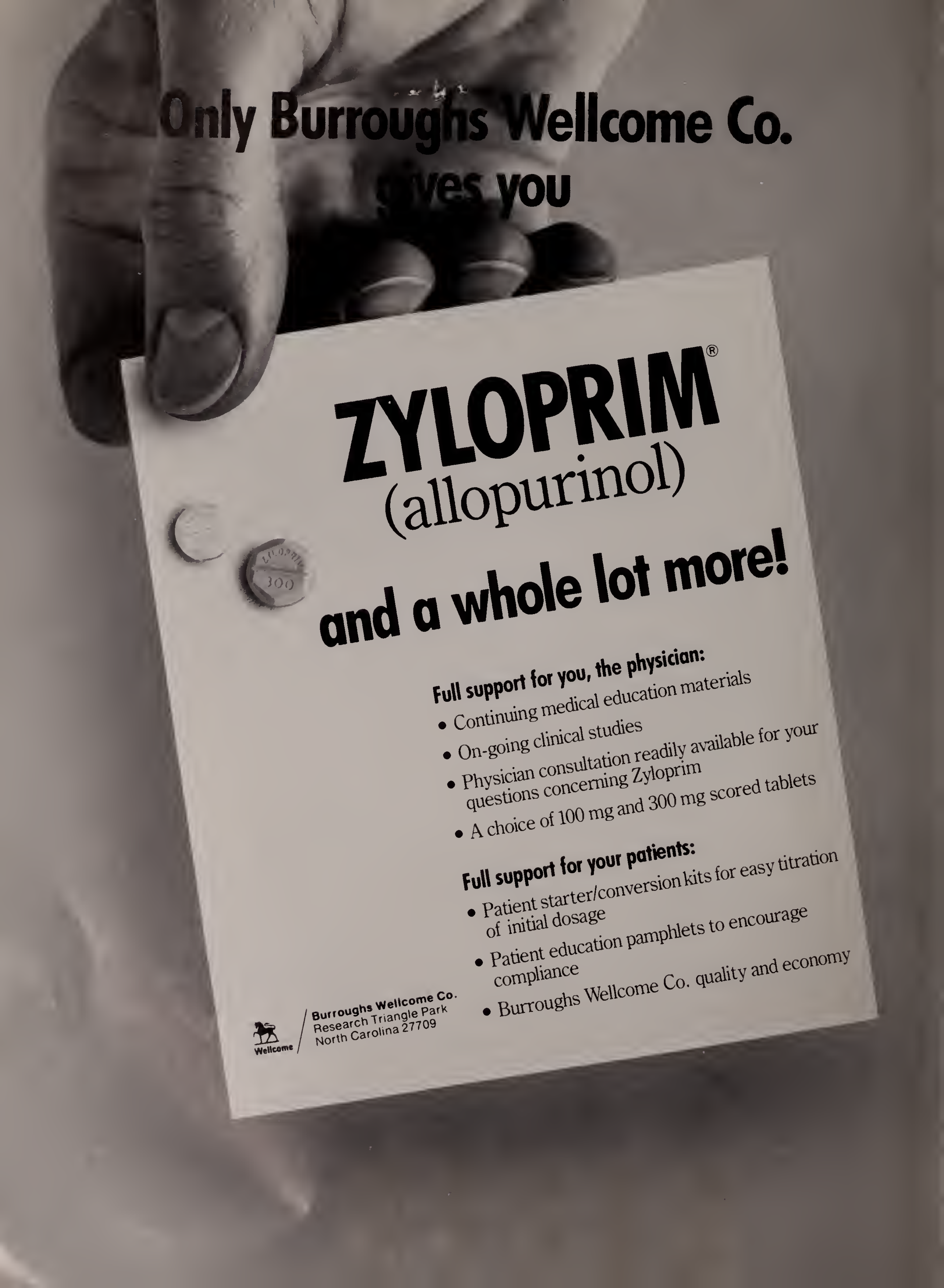

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from
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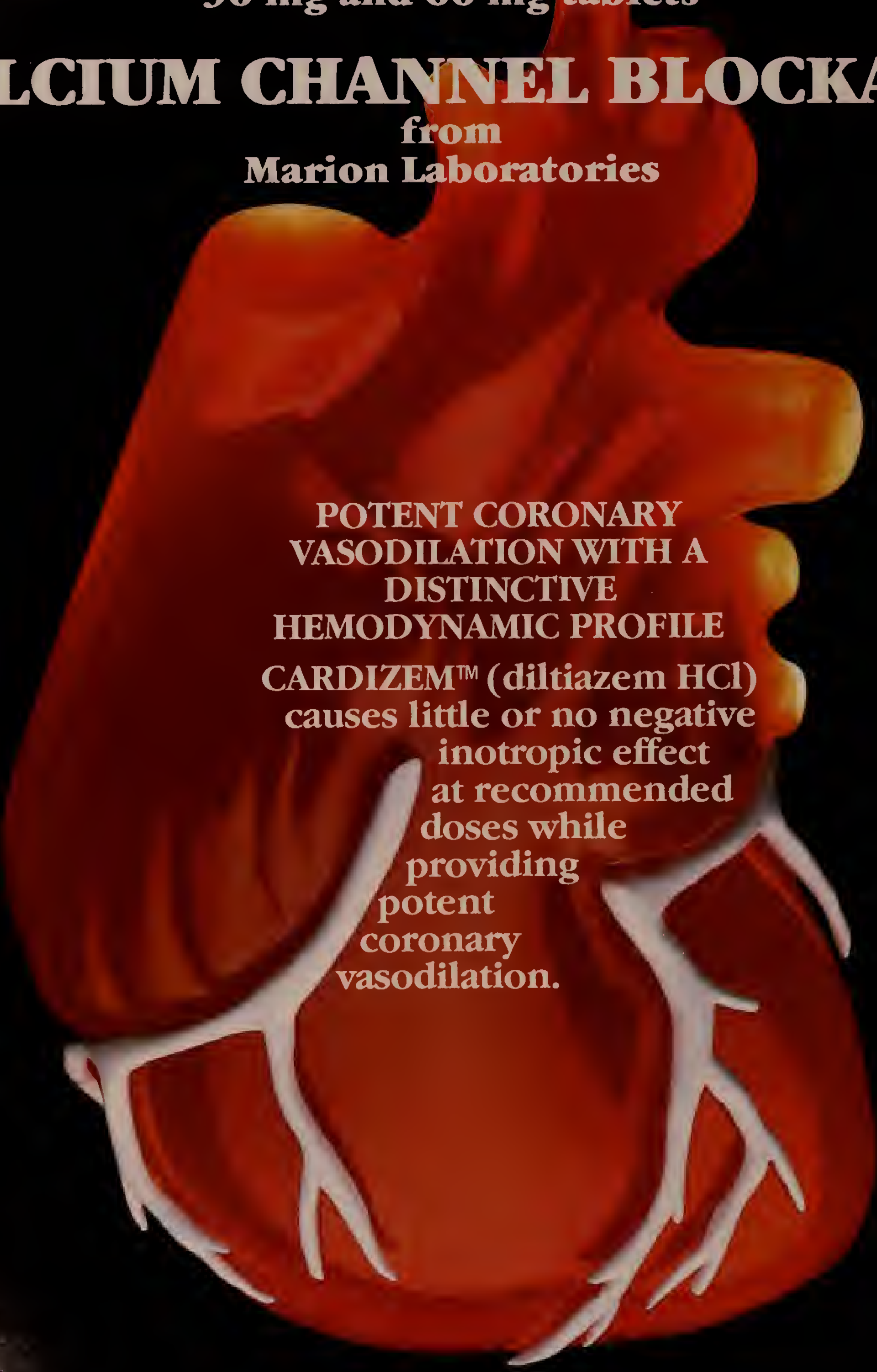

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CARDIZEM™ (diltiazem HCl) causes little or no negative inotropic effect at recommended doses while providing potent coronary vasodilation.

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(diltiazem HCl)
30 mg and 60 mg tablets

INCREASES EXERCISE TOLERANCE, REDUCES ANGINAL FREQUENCY* WITH A LOW INCIDENCE OF SIDE EFFECTS

Calcium channel blockade with CARDIZEM™ (diltiazem HCl) produces changes in cardiovascular hemodynamics and coronary blood flow that are of benefit in myocardial ischemia.

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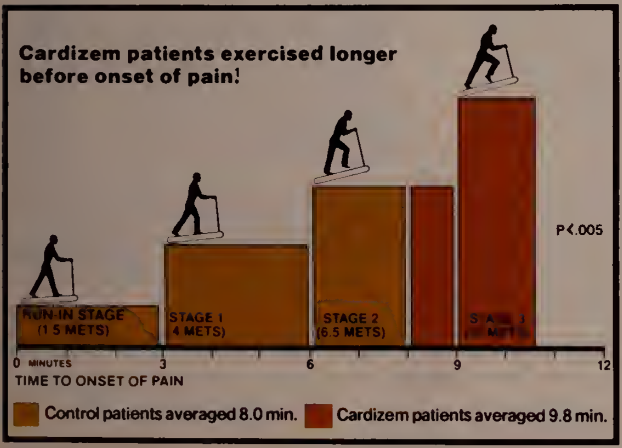

This study is of special significance because patients not only exercised longer but *to the next higher stage* in the Bruce protocol.

A Bruce protocol with a run-in stage was used for all tests. Each stage lasts three minutes.

In other studies, Cardizem produced 41% to 68% reduction of Prinzmetal's variant angina attacks[2]

†This study is a report from one center in a multicenter study.

Therapy with Cardizem produced a low incidence of side effects.

In placebo-controlled trials (222 patients) conducted in the United States, the incidence of adverse reactions reported during Cardizem therapy was not greater than that reported during placebo therapy.

Those adverse reactions reported most frequently with Cardizem in 959 patients in controlled and uncontrolled U.S. trials have been:

• Nausea	2.7%
• Swelling/edema	2.4%
• Arrhythmia	2.0%
• Headache	2.0%
• Rash	1.8%
• Fatigue	1.1%

Other reactions reported infrequently (less than 1%) are listed in full prescribing information on adjacent page.

**Please see adjacent page for full prescribing information.*

References:
1. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. *Chest* 78 (July suppl): 234-238, 1980.
2. Schroeder JS, Feldman RL, Giles TD, et al: Multiclinic controlled trial of diltiazem for Prinzmetal's angina. *Am J Med* 72:227-232, 1982.

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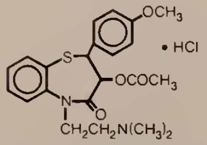
PROFESSIONAL USE INFORMATION

cardizem™
(diltiazem HCl)
30 mg and 60 mg tablets

DESCRIPTION

CARDIZEM™ (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+) -cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate/blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent as a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents. CARDIZEM has been effective in short-term controlled trials in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness is incomplete.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (four of 959 patients for 0.42%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** There has been a single report in a patient receiving 120 mg of diltiazem tid of marked transaminase elevation (SGOT 4500, SGPT 2300) accompanied by hyperbilirubinemia (to 3 mg%), occurring after four days of treatment. The enzyme abnormalities resolved entirely, and enzymes were nearly normal a week after cessation of treatment. No rechallenge was carried out, but the patient had no evidence of viral hepatitis and received no other drugs but isosorbide dinitrate.

   No other similar liver injury has been reported in clinical trials, but marketing experience in Europe has resulted in a rechallenge-confirmed instance of hepatocellular injury. However, it should be noted that there have been further episodes of raised transaminases in the absence of diltiazem in this patient, so that the relationship to diltiazem of the abnormalities is not completely clear. Other instances of transaminase elevation have been reported in Europe, but their relationship to the drug is uncertain.

PRECAUTIONS

General. CARDIZEM is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS.)

Uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities; the effect of diltiazem on serum digoxin levels has not been examined. The safety of the combination of CARDIZEM and beta-blockers or digitalis is currently being investigated in well-controlled studies.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded. Experience with an added beta-blocker is also extremely limited.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

In addition, the following have been reported infrequently and represent occurrences which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are nausea (2.7%), swelling/edema (2.4%), arrhythmia (2.0%), headache (2.0%), rash (1.8%), and fatigue (1.1%). In addition, the following events were reported infrequently (<1.0%). The order of presentation corresponds to the relative frequency of occurrence.

Cardiovascular:	Flushing, congestive heart failure, bradycardia, hypotension, syncope, pounding heart.
Central Nervous System:	Drowsiness, dizziness, lightheadedness, nervousness, depression, weakness, insomnia, confusion, hallucinations.
Gastrointestinal:	Vomiting, diarrhea, gastric upset, constipation, indigestion, pyrosis.
Dermatologic:	Pruritus, petechiae, urticaria.
Other:	Photosensitivity, nocturia, thirst, paresthesias, polyuria, osteoarticular pain.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

Experience in 959 patients taking oral doses of CARDIZEM resulted in three cases (0.31%) of second-degree AV block and one case (0.10%) of third-degree AV block at doses of 240 to 360 mg daily.

In rare instances, mild to moderate transient elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK have been noted during CARDIZEM therapy. A single incident of markedly elevated liver enzymes associated with symptoms was reported in a patient taking 360 mg per day for four days. Drug was discontinued and enzymes normalized within 1 week.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experiences with oral diltiazem have not been reported. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually to 240 mg (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. The effectiveness and safety of dosages exceeding 240 mg per day are currently being investigated. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents.

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

CARDIZEM 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

Issued 11/82

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PHYSICIANS WANTED

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OPERATING CORPORATION of several medical centers providing primary care for senior citizens seek board certified or board eligible, Florida licensed M.D.'s with the following specialties—family practice, internist, cardiologist and radiologist. Salary plus incentive. Insurance paid. Association fees paid. Contact Mr. Ed Hoke, H.S.C. Medical Centers, 1529 U.S. 19 South, Levitz Center, Clearwater, Fl. 33546. Phone (813) 530-9455.

FAMILY PRACTITIONER WANTED to establish solo practice in growing rural/suburban community located on Lake Ontario a short commute from Rochester, New York. Cultural, educational and recreational opportunities abound. Affiliation with 72 bed acute care hospital undergoing major building program. Income guarantee, rent and overhead subsidies negotiable. Contact: Robert Walcott, Jr., Executive Director, Lakeside Memorial Hospital, Brockport, New York 14420

OBSTETRICIAN & GYNECOLOGIST—needed for expanding HMO in southern California. Multispecialty group with facilities in Los Angeles and Orange Counties. CV to: Director/Physician Recruitment, CIGNA Healthplans of California, 700 N. Brand Blvd., Suite 500, Glendale, CA 91203.

INTERNIST, BOARD CERTIFIED, to join established internist, northern New York. Subspecialty added advantage. Reply Dept. 345, c/o NYSJM.

FULL TIME E.D. position available for career oriented Emergency Physician to join 4 other full time physicians in active Emergency Department of a 300 bed community hospital with excellent specialty coverage. Prefer board eligible or certified in emergency medicine. Must be ACLS or ATLS certified. Remuneration and fringe benefits competitive. Contact C.D. Hicks, Physician Procurement Committee, 157 Ross Street, Auburn, N.Y. 13021, (315) 253-3388.

WANTED INTERNIST, NASSAU Co., NY. Board certified/eligible, with/without subspecialty to join growing private practice. Reply Dept. 344, c/o NYSJM.

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MULTI-SPECIALTY SURGICAL GROUP in New Jersey has opportunities for: vascular surgeon, urologist, orthopedist, pediatric surgeon, head and neck surgeon. Must have or be eligible for New Jersey license. All operating expenses paid. Write to New Jersey Physician Placement Service, Box 252, Fair Lawn, New Jersey 07410.

WANTED: GENERAL INTERNIST to join present internist in a large hospital and office based practice in small community 1¼ hours from Rochester and 1¾ hours from Buffalo. Experience in Endoscopy and temporary pacemakers desirable but not essential. Reply Dept. 346, c/o NYSJM.

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MEDICAL PRACTICE AND HOUSE for sale. Long established Internist's practice in Poughkeepsie, New York includes large elegant home with fully equipped office in historic district. Must sell due to illness. (914) 454-2385.

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OPHTHALMOLOGIST, BOARD CERTIFED, F.A.C.S, F.I.C.S.: wishes to purchase practice in Manhattan. Strictly confidential. Reply to Dept. 294, c/o NYSJM.

OPHTHALMOLOGIST, BOARD Certified F.A.C.S, F.I.C.S., desires to purchase ophthalmology practice in Manhattan. Strictly confidential. Reply to Dept. 306, c/o NYSJM.

INTERNIST seeking partnership—group or private. NYC vicinity, Long Island or New Jersey. Evening (212) 209-1179; day (212) 381-1000.

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ANESTHESIOLOGIST: 15 years experience in all types of anesthesia. Trained in a major NYC teaching institution. Board eligible, conscientious, hard-working, excellent references. Willing to relocate. Reply Dept. 342 c/o NYSJM.

EQUIPMENT

COMPUTERIZED IBM ECG Aquisition and Analysis System—Model 5880 complete with programs. Single and dual disc units available. New January 1984. Phone 8am–10:30am or 4pm–7pm (212) 737-2023.

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Start with 80 mg once daily... Dosage may be increased to 120 mg or 160 mg once daily as needed to achieve additional control. Please see next page for further details and brief summary of prescribing information.

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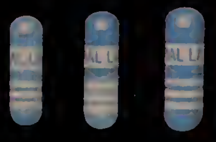

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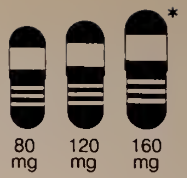

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)*
INDERAL* LA brand of propranolol hydrochloride **(Long Acting Capsules)**

DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.

CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period

The mechanism of the antihypertensive effect of INDERAL has not been established Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain.

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL

WARNINGS. CARDIAC FAILURE Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible)

> IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors

MAJOR SURGERY The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e g , dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker In one case this resulted after an initial dose of 5 mg propranolol

PRECAUTIONS. *General:* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies

Beta adrenoreceptor blockade can cause reduction of intraocular pressure Patients should be told that INDERAL may interfere with the glaucoma screening test Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about [illegible] times greater than the maximum recommended human dose

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Nursing Mothers: INDERAL is excreted in human milk Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia, visual disturbances, hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Auto-Immune. In extremely rare instances, systemic lupus erythematosus has been reported

Miscellaneous alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval

HYPERTENSION—*Dosage must be individualized* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved The usual maintenance dosage is 120 to 160 mg once daily In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks

ANGINA PECTORIS—*Dosage must be individualized* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized* The initial oral dose is 80 mg INDERAL LA once daily The usual effective dose range is 160-240 mg once daily The dosage may be increased gradually to achieve optimum migraine prophylaxis If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued It may be advisable to withdraw the drug gradually over a period of several weeks

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use

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8950/284

Just once each day...

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JOURNAL OF MEDICINE

June 1984 • Volume 84, Number 6

COMMENTARIES

The Hypertension Detection and Follow-up Program

In an article in this issue of the *Journal*[1] Drs Schnall, Alderman and Kern have analyzed data from a report by a member of the Hypertension Detection and Follow-up Program (HDFP).[2] They arrive at two conclusions which are markedly divergent in their implications: (1) the HDFP trial showed that antihypertensive treatment of white women with moderate and severe hypertension had adverse effects, and (2) Based on the known limitations of subgroup analysis, the findings can not be interpreted as definitive evidence for or against antihypertensive treatment of white women with moderate and severe hypertension.

The Hypertension Detection and Follow-up Program was designed to determine if a systematic approach to antihypertensive therapy would lower all-cause mortality. The sample size was adequate to test the hypothesis for the entire group and for Stratum I (diastolic blood pressure (DBP) of 90 to 104 mm Hg).[3] The sample size was not adequate to test the hypothesis for the entire population of moderate and severe hypertensive individuals and certainly not for one race and sex subset. Moreover, the more severe the hypertension at baseline, the less the difference in death rate following antihypertensive therapy between the Stepped and Referred groups. The Referred group was treated energetically, especially the more severe cases. The small difference in mortality rate following therapy would have attenuated even further the power of the study if these small groups had been considered as representing a primary part of the study that required separate analysis.

There remains, however, the observation that all-cause mortality was higher in the white women Stepped Care participants with DBP $\geq$ 105 mm Hg than in the corresponding Referred Care participants. What does this suggest?

As I, a clinician, began my tenure as chairman of the HDFP, I learned an important concept from Maureen Henderson, MD, an epidemiologist. It deals with data used for testing hypotheses and data used for generating new hypotheses. An example of hypothesis testing is that of the HDFP or other clinical trials, or indeed any approach in which one independent group is compared with another group to test a previously-proposed hypothesis. Dr Schnall and his colleagues have used a hypothesis-generating approach, in which by subset analysis one may find results discordant with the expectations of the entire trial. A hypothesis is then proposed to explain this discordance. There is a very definite possibility that the discordant results could have occurred by chance in this kind of analysis. However, if the hypothesis is plausible, then it is worthwhile to do further studies to determine its validity.

I understand the authors' hypothesis to mean the following: whereas effective antihypertensive medication lowers all-cause mortality rates, it is dangerous in white women with basal DBP $\geq$ 105 mm Hg. There is a logical complement to this hypothesis: intensive antihypertensive therapy, as delivered by the Stepped Care approach, is significantly beneficial in white women with DBP 90 to 104 mm Hg. This is based on subgroup analysis which demonstrated "significantly" less mortality (without correction for baseline imbalance and multiple testing) in the Stepped Care group than the Referred Care group for this subset. The implication is that this antihypertensive therapy is dangerous despite the reduced mortality rate in the Stepped Care group overall, and despite the beneficial response to therapy in a Veterans Administration study of moderate to severe hypertension in men, in which the same blood pressure levels as in the HDFP are used.

Due to these conflicting results I find the authors' hypothesis extremely improbable. However, it is important to examine some data that were not available to Dr Schnall et al at the time of their study.

First, based on the number of individuals in the population that were identified as having hypertension, the percentage of white females that entered the HDFP was much smaller than for other race/sex groups. The subgroup of white females was aberrant from the outset. They had a variety of diseases, and chance imbalance of these morbid conditions could have a large influence on total mortality.

Second, there was very little difference between the Stepped Care and Referred Care groups in the antihypertensive therapy administered to the white women. By the fifth year, 96 percent of the surviving white women in Stepped Care with DBP of 104 mm Hg were on antihypertensive medication, compared to 88 percent in Referred Care. If Stepped Care was lethal, so should Referred Care have been.

In addition, there was little use of beta blocking agents in either group and only a minimal difference in serum potassium.

Finally, further evidence to suggest that intensive therapy was not lethal comes from an examination of the last recorded blood pressures before death in Stepped and Referred Care patients. These blood pressures were higher than the mean of their group, although the Stepped Care participants who later died had slightly lower pressures than the Referred Care participants who later died. However, the Stepped Care participants who later died had higher pressures than the remainder of the Referred Care participants.

Hypertension is a major cause of cardiovascular mortality and morbidity. Therefore, the conclusions that are drawn from studies such as the HDFP have enormous importance. There is a large body of data to support the view that antihypertensive therapy lowers mortality and morbidity. This opinion on the value of antihypertensive medication should not be considered as dogma, but neither should it be attacked without due consideration. I began with the opinion that Dr Schnall and his colleagues had chosen an unlikely hypothesis and supported it with chance variation based on subgroup analysis; however, I believe the opposite had occurred—they noted chance variation and used it as a basis for an unlikely hypothesis. Ironically, the authors picked a subset of individuals with blood pressures so high that given an adequate sample size and had there been a significant difference in the mortality rates of the Stepped and Referred Care groups, the results would have had such powerful prognostic implications that the effects of other yet to be specified criteria would have been masked.

I would also like to raise a few technical objections to the authors' paper. The statements that the Stepped and Referred Care groups of women were unlikely to be significantly different from each other, since randomization of subjects was employed, and that the overall groups were virtually identical are incorrect. Randomization does not assure that every subgroup will be well-matched for all important variables. In subgroup analyses, one must look at all the important variables, which the authors did not do. For example, the numbers at risk figures show that the Stepped Care group had 38 more white women than Referred Care.

The authors are incorrect in stating that the magnitude of the Z-score changes depending on the use of a one-sided or a two-sided test of a hypothesis. In fact, it is the probability (*P*) that changes.

The authors imply that they have used the more conservative two-sided test of a hypothesis when, in fact, the *P* values they report are based on a more liberal one-sided test. Furthermore, if one views the subgroup discussed by the authors, it is only one of eight race/sex/blood pressure groups. If one group is tested, then all eight should be tested. There is a 34% chance that one or more of the tests will yield a *P* value less than or equal to 0.05 by chance alone.

The more appropriate approach to selecting specific subgroups for special analysis is to test for evidence of interaction in the data. This is not the approach the authors used. Rather, they identified a selected subgroup based on the observed data, then formulated a hypothesis and tested it on that same set of data. Furthermore, the statement that "cardiac mortality" was greater in the Australian and United States Public Health Service trials in treated subjects is incorrect.

The authors' logic leads to the following conclusion: white women with severe hypertension should not be treated. I cannot believe that the authors hold this view, and if they do not, then their argument becomes a pale and flaccid exercise.

HERBERT G. LANGFORD, MD
Chairman, Steering Committee
Hypertension Detection and Follow-Up Program
National Heart, Lung, and Blood Institute
National Institutes of Health
Professor of Medicine
University of Mississippi Medical Center
Jackson, Mississippi 39216

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1. Schnall PL, Alderman MH, Kern R: An analysis of the HDFP trial. Evidence of adverse effects of antihypertensive treatment on white women with moderate and severe hypertension. *NY State J Med* 1984; 84:299-301.
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Interpreting randomized trials

Schnall et al[1] raise provocative issues in their reanalysis of the Hypertension Detection and Follow-up Program (HDFP). Quoting data presented at a conference on mild hypertension and published in the *Transactions of the Association of Life Insu Medical Directors of America*,[2] these authors suggest that Caucasian women with diastolic pressures above 105 had a significantly higher mortality rate if placed in the Stepped Care group. The Stepped Care group was offered systematic, controlled antihypertensive treatment, whereas patients in the Referred Care group were referred to their regular sources of health care.

One problem with the authors' reanalysis is the multiple comparison bias (the limitations of subgroup analysis). The authors were aware of this bias and as a result tempered their conclusions.

This kind of bias occurs when searching through data to find differences that appear significant. Some large differences will occur due to chance alone. If these are detected, the nominal probability associated with a chance finding will no longer apply. Even if no difference existed in the population between the Stepped and Regular Care groups, 5 of 100 trials will show a significant difference that is due to chance. The same applies to comparisons among 100 subgroups in a single trial.

In the HDFP trial comparisons were made between three blood pressure groups, four race/sex-specific groups, and three age groups. This produces 36 subgroups to compare between Stepped and Referred Care and a high likelihood that one or two comparisons will be significant by chance, even if there are no real differences in the population.

Another difficulty in interpreting subgroup analysis is illustrated by the following paradox. In the HDFP trial there was no difference in overall mortality between Caucasian women by treatment group. Accordingly, if women with diastolic pressures of 105 or more in the Stepped Care group are at greater risk, as the authors proposed, than women with lower pressures in the Stepped Care group must be at lesser risk. In fact, the latter women had a 41 percent lower mortality rate (3.6) than women in the Referred Care group (5.1). Although the difference was not statistically significant, it could have biological importance especially since the sample sizes were not selected to detect differences in subgroups. Thus, the reanalysis suggests that antihypertensive therapy may benefit women with mild hypertension but may be harmful for those with more severe hypertension. The authors offer no explanation for this inconsistency.

An example of a spurious finding from subgroup analysis is illustrated by the Multiple Risk Factor Intervention Trial (MRFIT).[3] In this trial no difference was detected between the Stepped Care group (intervention to reduce smoking, cholesterol and blood pressure) and the usual care or Referred group. The authors of MRFIT attribute the absence of a difference between the groups to an aberrant subgroup: Men with abnormal electrocardiograms (ECG) who were treated for hypertension in the Stepped Care group had an unexplained high death rate. However, a special analysis of the HDFP data did not confirm this unusual finding.[4]

Are the problems of subgroup analysis so great that this approach should be disregarded? I think not. Clinical trials are too expensive and the consequences of adverse side-effects too serious not to explore fully all the data. Furthermore, it is the subgroup analysis that enables the physician to judge whether a particular patient will benefit from a specific therapy. Herein lies one serious dilemma in the interpretation of clinical trials.

The answer lies in part with replication and in part with biological plausibility. Replication refers to obtaining similar results in other trials. The higher death rate of men with ECG abnormalities in the MRFIT trial was not verified in the HDFP trial. Therefore, the finding must be questioned. In the present reanalysis, the higher mortality rate seen in Caucasian women with blood pressures of 105 or higher and in Stepped Care takes on added significance, since other trials have failed to show a benefit of antihypertensive therapy for women.[5] Previous studies have suggested that hypertension in women, even if untreated, has fewer complications and is less serious than in men.[6,7]

Under these circumstances, the authors' cautions about the diverse effects of a standard therapeutic regimen are well made.

JOSEPH FELDMAN, DrPH
Associate Professor
Department of Preventive Medicine
and Community Health
State University of New York
Downstate Medical Center
Brooklyn, NY 11203

1. Schnall PL, Alderman MH, Kern R: An analysis of the HDFP trial: Evidence of adverse effects of antihypertensive treatment on white women with moderate and severe hypertension. *NY State J Med* 1984; 84:299-301.
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Emerging importance of infections due to the *Mycobacterium avium-intracellulare* complex

Robert Koch's discovery of the tubercule bacillus in 1882 was followed by descriptions of many other mycobacteria and recognition of their role in disease in animals. The role of these organisms in human disease remained uncertain until much later. During several decades, a small number of presumed tuberculosis cases were identified as different and puzzling because their acid-fast bacilli were not pathogenic for guinea pigs. The improved culture methods developed and used during the 1950s enabled the recognition and classification of these organisms in human disease. Even then, mycobacterial infections other than tuberculosis accounted for only 1% to 3% of tuberculosis cases.

In recent years the picture has changed. The incidence of tuberculosis has declined steadily, but in many regions of the country other mycobacterial diseases, especially those due to the *Mycobacterium avium-intracellulare* complex (MAI), have markedly increased relative to tuberculosis and in absolute numbers as well. Most such cases present as indolent chronic pulmonary infections in middle aged and older men with pre-existing lung disease, especially chronic obstructive pulmonary disease. A different type of MAI disease occurs in early childhood, presenting as cervical lymphadenitis. In both the pulmonary and lymph node types, the disease is characteristically localized; extrapulmonary or disseminated forms of the disease are rare except in compromised hosts (patients with advanced cancer or taking immunosuppressive drugs).

With the current epidemic of acquired immunodeficiency syndrome (AIDS), a new aspect of mycobacterial disease has emerged. *M avium-intracellulare* organisms are ubiquitous in the environment, and most individuals are exposed to them from time to time without harm. The patient with AIDS responds to these encounters poorly, however. In up to half of all patients with AIDS there is mycobacterial disease—some with tuberculosis but more with MAI—involving the gastrointestinal tract as well as the lungs. Disseminated disease is also frequent. The histopathologic response is unusual—granulomas are poorly formed, if at all, and large numbers of acid-fast bacilli are found in tissue biopsies. Mycobacterial disease contributes strongly to morbidity and mortality in patients with AIDS, both indirectly and directly. The indirect effect is due to functional impairment of the gut with malabsorption and nutritional depletion which is common in the later stages of AIDS.

The case presentation of George et al[1] in this issue of the *Journal* shares many features of AIDS cases, and there is a reasonable likelihood that it was a form of AIDS. If so, such cases will be seen with some frequency in many hospitals, and awareness leading to accurate diagnosis is important. The incidence of AIDS may have declined recently from its peak, but this disease is likely to be with us for some time to come.

The treatment of these infections leaves a lot to be desired because of nearly complete in vitro resistance to anti-tuberculosis drugs. Fortunately, infection in the patient without AIDS is one of modest extent with a reasonably good outlook using standard antituberculosis drugs or no chemotherapy at all. Surgery has shown favorable results in selected good-risk patients with disease localized to one lobe or less. Surgery to excise the affected tissue is also the treatment of choice in childhood cervical lymphadenitis.

More advanced or progressive disease or that seen in patients with AIDS represents a real therapeutic challenge, however. The recommended approach is a multiple, four to six drug regimen. Experience at larger centers suggests that combinations of rifampin, ethambutol, ethionamide, cycloserine, and streptomycin or kanamycin may be effective. With these drugs, a high incidence of toxic reactions can occur which unfortunately limits the practicality and effectiveness of this approach. Two newer agents show promise. The experimental drug Ansamycin LM427 shows a high level of effectiveness in vitro, and limited success has been seen in clinical use in patients with AIDS. Clofazimine, an anti-leprosy agent, also is effective in vitro. It concentrates well in the reticuloendothelial tissues but poorly in the lungs, so its role should principally be for extrapulmonary and disseminated disease.

Infections due to MAI have emerged from being a small part of tuberculosis practice to the mainstream of clinical medicine. Despite our current limitations in effective treatment, recognition of these infections and their differentiation from tuberculosis is important.

DAVID Y. ROSENZWEIG, MD
Associate Professor of Medicine
Medical College of Wisconsin
Milwaukee, WI 53226

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[1] George TK, Schuster RJ, Wood JB: Disseminated infection with *Mycobacterium avium-intracellulare*. *NY State J Med* 1984; 84:319-320.

An overview of *Mycobacterium avium-intracellulare*

Many species of mycobacteria have been identified in nature. Few of these are well adapted to a parasitic or symbiotic existence in man and animals. The usual human pathogens *Mycobacterium leprae*, *M tuberculosis* and *M bovis* are well known. A number of others, however, may cause infection and sporadic disease in man. The latter seem to require special circumstances for growth. They simulate tuberculosis in terms of pathology and clinical presentation.

These organisms vary in geographic distribution, and hence there is much local variation in the prevalence rates of the diseases they cause. The organism *Mycobacterium avium-intracellulare* is one of a variety of organisms that behave in this manner. Some of these groups cause disease in swine and others in fowl. In experimental situations they did not cause disease in guinea pigs but did in mice. It seems that *M avium-intracellulare* is the only bacterium in the so-called Runyon group III that may cause significant progressive disease in man. In general, however, the bacterium seems to have little pathogenicity for man, because the organism has a wide distribution, but human disease is rare.

Most disease occurs because of an underlying condition of the lung such as pneumoconiosis or bronchitis. Cervical adenitis as a de novo disease due to *M avium-intracellulare* is well known in children, especially of school age. Disseminated disease, though rare, may occur, as illustrated by the case reported by Timothy George et al[1] in this issue of the *Journal*. *M avium* has been isolated from sites in the body where attempts at repeat isolation fail. In such instances the isolation is not significant.

Human infection with this group of bacteria is common and in some areas rivals tuberculosis infection. These infections occur in tropical, temperate and subtropical zones and are common in New York State. When testing with antigen specific for *M avium-intracellulare* one obtains cross reactions with purified protein derivative (PPD)-S. The latter however gives fewer cross reactions with PPD-B (avium). Delayed hypersensitivity due to PPD-B is probably greater than 10 percent in the New York State population.

The incidence of disease due to this organism varies in the United States from one place to another. In some localities it is found more frequently than tuberculosis. Treatment entails the administration of a combination of from four to six antimicrobial agents over a prolonged period of time.

ALJE VENNEMA, MD
Director
Bureau of Tuberculosis Control
The New York City Department of Health
New York, NY 10013

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[1] George TK, Schuster RJ, Wood JB: Disseminated infection with *Mycobacterium avium-intracellulare*. *NY State J Med* 1984; 84:319–320.

Tumors of the appendix

Considering the small size of the appendix and the rarity of primary appendiceal adenocarcinoma (less than 0.01% of resected appendices)[1] and carcinoid tumor of the appendix (approximately 0.1% of resected appendices) the case reported by Drs Fleisher, Gordon and Pascal[2] in this issue of the *Journal* is remarkable. The authors' patient, who presented with acute appendicitis and a mass in the right lower quadrant, had two separate and histologically different appendiceal neoplasms—one a carcinoid and the other a microglandular adenocarcinoma. Luminal obstruction by one of the tumors had apparently given rise to appendicitis, a symptom of the majority of adenocarcinomas of the appendix. Parenthetically, in an elderly patient presenting with appendicitis, the possibility of a neoplastic process in the cecal region should be considered.

The microglandular or signet ring type of adenocarcinoma may escape detection by the pathologist, as its cells are pale-staining and inconspicuous,[1] particularly against a background of an acutely inflamed appendix. However, this is a fully malignant neoplasm with the potential to grow along nerve fibers and peritoneal surfaces, to metastasize to regional lymph nodes and, in female patients, to metastasize to the ovaries. In the case reported by Fleisher et al, ileocolectomy was performed as a second procedure, for treatment (and staging) of the adenocarcinoma. Fortunately no residual or metastatic carcinoma was discovered in the patient, although the condition of the ovaries was not specified. The original appendiceal cancer involved the entire thickness of the wall; in the absence of nodal metastases it would be a Dukes Stage B.

Carcinoids, meaning carcinoma-like tumors, were first described in 1907 by Oberndorfer.[3] In the 1960s a number of reports of ordinary carcinomas with some features of carcinoid were reported in tumors of the stomach,[4] colon,[5] rectum[6] and appendix.[5] During the next decade, the designation of "mucinous carcinoid tumor," [7] "goblet cell carcinoid"[8] or "adenocarcinoid"[9-11] was used to refer to a distinctive tumor of the appendix, characterized by small glands with signet ring cells and sometimes showing argyrophilic granules or Paneth cells or both. By light microscopy this tumor is identical to microglandular carcinoma.

The belief that goblet cell carcinoid, mucinous carcinoid or adenocarcinoid tumors are variants of the carcinoid has been challenged by Isaacson,[12,13] who studied classical carcinoids and adenocarcinoids using histochemical stains, with normal intestinal mucosa as a control. He demonstrated that the cells of adenocarcinoids were analogous to crypt cells of intestinal epithelium; included among crypt cells are occasional Kulchitsky cells, the neuroendocrine cells from which true carcinoid tumors are thought to originate. Isaacson argued that "carcinoid" should not be a part of the name for the distinctive small gland-forming tumor and suggested a new name, "crypt cell carcinoma." In the case reported by Fleisher et al a series of histochemical and immunohistochemical studies showed that microglandular carcinoma is not related to ordinary carcinoid tumor.

It is of more than academic interest to understand the biological nature of microglandular tumors of the appendix. Whereas appendiceal carcinoid tumors metastasize with the utmost rarity, without threat to the life of the patient,[14] microglandular (crypt cell) carcinomas of the appendix require surgery, such as was performed on the patient reported by Fleisher et al.

MARIANNE WOLFF, MD
Director of Surgical Pathology
Morristown Memorial Hospital
Morristown, NJ 07960

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Management of hyperparathyroidism in pregnancy

Clinical observations over many years have documented severe difficulties associated with hyperparathyroidism complicating pregnancy.[1] Neonatal tetany, fetal death, and premature births are noted to occur with unacceptable frequency, although cases in the literature undergo an intense selection process and therefore are probably biased.[2]

As has been demonstrated in elegant animal experiments by Taylor and colleagues,[3] maternal hyperparathyroidism damages the fetus by suppression of the fetal parathyroid glands, since calcium freely crosses the placenta from the hypercalcemic mother.

The report by Gershberg and Young[4] in this issue of the *Journal* details the successful surgical management of hyperparathyroidism during pregnancy. Numerous similar reports are cited by these authors. Management of this situation with oral phosphate has also been reported,[5] and some pregnant patients with mild hyperparathyroidism have been observed to require no treatment, without morbidity to mother or offspring.[2,6,7] No data from prospective, controlled studies of humans are available or are likely to be obtainable in the future given the relative rarity of the condition.

Thus, considerable latitude for individual judgment exists in the management of these patients. A balanced approach to the problem can be formulated as follows. Serum calcium levels should be monitored early in a pregnancy if there is any previous episode or family history of kidney stones or suggestive symptoms. It should be recalled that the normal serum calcium level for a pregnant woman is lower than the normal level for a non-pregnant woman. Therefore, values in the upper normal range should raise suspicion. A diagnosis of hyperparathyroidism, however, requires the exclusion of other causes of hypercalcemia and an assessment of serum phosphorus and serum parathyroid hormone levels. Ultimately, the diagnosis must rest on clinical grounds. Many difficulties arise if too much reliance is placed on laboratory measurements.[8]

If the patient's medical course is to be followed, close observation of the gestation as a high risk pregnancy is justified, in my opinion. The neonate will also require close monitoring if not intensive care.

Neck exploration is advisable for those patients with hypercalcemia above the mildly elevated range or with obvious physical deterioration such as worsening renal function or osteitis fibrosa cystica. These recommendations are similar to those offered by Coe and Favus[9] for non-pregnant patients with mild hyperparathyroidism. Parathyroidectomy should not be attempted by a surgeon as an occasional procedure in any patient.

Thus, the management of hyperparathyroidism in the pregnant patient will be a matter of highly individualized considerations, including the availability of an experienced surgeon. With a heightened awareness during recent years of the factors involved in caring for a pregnant patient with hyperparathyroidism, better treatment can be expected for both mother and newborn.

RICHARD F. GAEKE, MD
Department of Internal Medicine
Middletown Regional Hospital
Middletown, OH 45042

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At its April 1984 meeting, the Council of the Medical Society of the State of New York approved the following guidelines which were developed by an ad hoc committee at the behest of the council.

GUIDELINES FOR HOSPITALS AND PHYSICIANS ON "DO NOT RESUSCITATE"

The following are intended *only* to be guidelines for physicians and hospitals. Hospital medical staffs and governing bodies are encouraged to develop policies consistent with their respective by-laws and rules and regulations.

DEFINITION

DNR (Do Not Resuscitate) means that, in the event of a cardiac or respiratory arrest, cardiopulmonary resuscitative measures will not be initiated or carried out.

BACKGROUND

1. An appropriate knowledge of the serious nature of the patient's medical condition is necessary.
2. The attending physician should determine the appropriateness of a DNR order for any given patient.
3. DNR orders are compatible with maximal therapeutic care. A patient may receive vigorous support in all other therapeutic modalities and yet a DNR order may be justified.
4. When a patient is capable of making his own judgments, the DNR decision should be reached consensually by the patient and physician. When the patient is not capable of making his own decision, the decision should be reached after consultation between the appropriate family member(s) and the physician. If a patient disagrees, or, in the case of a patient incapable of making an appropriate decision, the family member(s) disagree, a DNR order should not be written.

IMPLEMENTATION

1. Once the DNR decision has been made, this directive shall be written as a formal order by the attending physician. A verbal or telephone order for DNR cannot be justified as a sound medical or legal practice.
2. It is the responsibility of the attending physician to insure that this order and its meaning are discussed with appropriate members of the hospital staff.
3. The facts and considerations relevant to this decision shall be recorded by the attending physician in the progress notes.
4. The DNR order shall be subject to review *at any time by all concerned parties* on a regular basis and may be rescinded at any time.

LETTERS TO THE EDITOR

Address correspondence to Editor, New York State Journal of Medicine, *420 Lakeville Road, Lake Success, NY 11042. Letters should be typed double-spaced and include the signature, academic degree, professional affiliation, and address of each author. Preference is given to letters not exceeding 450 words, and every effort will be made to assure prompt publication. All letters are personally acknowledged by the Editor.*

Debating authorship

TO THE EDITOR: I have just finished reading the case report in the *New York State Journal of Medicine* entitled "Single lung transplantation in paraquat intoxication" by Kamholtz et al (1984; 84:82–84), which has given new meaning to the term "et al."

The article, albeit interesting and well done, is certainly unique in the annals of medical literature in that this two and one-half page article (one page of which consists of illustrations), has 19 authors! In the current atmosphere of "publish or perish" it is not surprising that each contributor wants credit for his or her part in the article. Or, as Jimmy Durante used to say, ". . .*everybody* wants to get into the act."

MAURICE E. SHERMAN, MD
880 Fifth Avenue
New York, NY 10021

In reply: Clinical investigators, peer reviewers and journal editors must all share the very real concerns raised by Dr Sherman in his letter commenting on our recent case report "Single Lung Transplantation in Paraquat Intoxication." As a result of the progressive increase in the number of authors per article in medical journals, numerous guidelines for authorship have recently been proposed.[1-3] Clinical situations in which prolonged multidisciplinary input and expertise are essential to the management of particularly complex patients are also increasingly common.

Prior to acceptance of this paper for publication, the editor of the *Journal* questioned the long list of coauthors appended to this report; however, we provided evidence that rigid guidelines had been employed in the determination of coauthorship. We applied Fishbein's suggestion that "if a person has rendered service of major importance, his name should be included with those of the authors of the paper."[4] The sequence of placement of authors' names follows the guidelines proposed by Burman[1] in the *Annals of Internal Medicine.* We heartily agree with Relman[5] who believes that coauthorship denotes "meaningful participation in planning, design and interpretation," and we have strictly applied these tenets in the preparation of our case report. Until other forms of recognition for extensive participation in the management of complex cases become widely accepted,[3] the literature will continue to be sprinkled with reports that *appropriately* list as many as 19 coauthors.

STEPHAN L. KAMHOLZ, MD
Associate Professor of Medicine
Co-Investigator,
Lung Transplantation Laboratory

FRANK J. VEITH, MD
Professor of Surgery
Director, Transplant and Vascular Surgery
Albert Einstein College of Medicine
Bronx, NY 10467

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Drug treatment of tuberculosis

TO THE EDITOR: The case report of Inselman et al[1] is of interest in pointing up the problem of chemotherapy where the infecting organisms are resistant to both isoniazid and rifampin. However, there are several unanswered questions in the report which are of vital interest in today's concept of tuberculosis control and treatment.

In their epidemiologic survey they report that no index case was found for the source case (father) but failed to mention whether other members of the family were investigated.

The use of two drugs to which the infecting organisms are resistant coupled with one susceptible drug is contrary to the recommendations of the Ad Hoc Committee of the Scientific Assembly on Microbiology, Tuberculosis and Pulmonary Infections and the Scientific Assembly on Pediatrics, of which the senior author of the report was a member.[2] This report states that "if neither isoniazid nor rifampin can be used, the patient must be given at least two and preferably three drugs to which his organisms are known to be susceptible. These drugs must be given for at least 18 months." Isoniazid has been included in drug regimens even when the organisms are resistant, but only in combination with two susceptible drugs.

The authors state that in their experience, isoniazid resistance has been low. Is this a clinical impression or is it substantiated by (unstated) data. Resistance rates reported during the past 20 years and drawn from the same community from which the Jewish Hospital and Medical Center of Brooklyn draws its patients, have been reported over four-year periods since 1961 and have been high.[3]

Finally, implications drawn from clinical success in the treatment of one case must be guarded unless it involves a lethal form of infection such as tuberculosis meningitis.

MORRIS STEINER, MD
Professor Pediatrics, Emeritus
State University of New York
Downstate Medical Center
450 Clarkson Avenue
Brooklyn, NY 11203

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In reply: Dr Steiner's comments are valid and appreciated. Several were addressed in the original manuscript submitted for publication but were omitted for brevity. I am therefore glad to have the opportunity to respond to these comments.

The patient's mother had a negative tuberculin skin test and chest x-ray, and her skin test reaction remained negative upon periodic retesting. There were no other individuals living at home, and the child was not known to have been exposed to anyone with tuberculosis other than her father.

In general, two drugs to which the organism is susceptible should be used in the treatment regimen. The recommendations of the committee to which Dr Steiner refers are intended only as guidelines. After consultation with several other physicians experienced in the treatment of childhood tuberculosis, isoniazid and rifampin were continued for several reasons. Despite in vitro resistance patterns, the clinical response may still be favorable. The bacillary load in the hip was felt to be low, and a high dose of isoniazid could be appropriate. The use of the second-line drugs, with their subsequent toxicities, is limited in children. Lastly, by the time the drug resistance pattern was available, clinical and radiologic improvement had occurred. Therefore, it appeared prudent to proceed with the three drugs used.

The prevalence of isoniazid resistance was low at Brooklyn Jewish Hospital and its Greenpoint Hospital affiliate. Between 1974 and 1980, we observed 17 children with systemic tuberculosis, none of whom had isoniazid resistance,[1] and more recently five systemic cases who also did not have isoniazid resistance. The basis for the disparity in the prevalence of isoniazid resistance between this medical center and Kings County Hospital is unknown. However, variations in the country of origin of the population may be a contributing factor. It is of interest to note that the isoniazid resistance rate of 4.5% at Kings County Hospital for 1977 to 1980[2] is comparable to the 4.9% rate in New York City for 1980.

This report of the therapeutic success of our patient was not intended to imply that this is the preferred regimen for all similar cases. Indeed, therapy should be individualized. It was felt that this was an unusual case of tuberculosis which would be of interest to newly-trained physicians who may not be aware of the variable presentations of childhood tuberculosis and problems encountered in treatment. It is hoped that this case report will encourage others to communicate their experiences with extrapulmonary tuberculosis and the therapeutic dilemmas that they have encountered.

LAURA S. INSELMAN, MD
North Shore University Hospital
Manhasset, New York 11030

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Traumatic midbrain hemorrhage demonstrated by computerized axial tomography

TO THE EDITOR: We report a case of a boy with traumatic injury to the brainstem presenting with functional decerebration and bilateral third nerve dysfunction, who survived and retained good cognitive function and residual midbrain damage. Serial CT scans demonstrated a discrete midbrain hemorrhage. Patients with brainstem contusion and hemorrhage can recover despite signs of severe midbrain dysfunction.

Case Report. On April 9, 1980 this 12-year-old boy was struck by a car. When examined in the emergency room minutes later, he showed weak withdrawal of all his extremities to noxious stimuli. Both pupils were fully dilated and unresponsive to light. Cold caloric stimulation to each side produced only abduction of the ipsilateral eye. Corneal reaction was positive in both eyes. Deep tendon reflexes were 2+ to 3+ and plantar responses were extensor. The child had sustained multiple fractures of the lower extremities. A CT scan showed partial obliteration of the quadrigeminal cistern suggesting midbrain swelling and small lateral ventricles. On the second hospital day, the patient showed purposeful withdrawal to noxious stimuli of all four extremities, with no change in the rest of the neurologic examination. On the seventh hospital day the patient developed hypertension with a BP in the range of 150 to 220 systolic and 100 to 130 diastolic. A repeat CT scan that day showed a discrete hemorrhage in the paramedian midbrain tegmentum (Fig 1). The hypertension persisted for several days in spite of therapy with multiple antihypertensive medications, with no deterioration in the patient's neurologic examination. The patient continued to show gradual improvement. After four weeks, he was easily aroused, responding to his name by opening his right eye. A repeat CT scan at this time showed mild cerebral atrophy with complete resolution of the midbrain hemorrhage. By five weeks he was following commands. He remained mute, with only an occasional outburst of speech when upset. His speech gradually improved, and after nine weeks, he was fairly fluent. The patient was walking with assistance at this time. Six months after his accident, he was attending school on a regular basis. Psychometric testing showed his performance to be at, or slightly below, grade level in all areas. He had residual bilateral third nerve palsies with mild bilateral hemiparesis, slightly more severe on the right side.

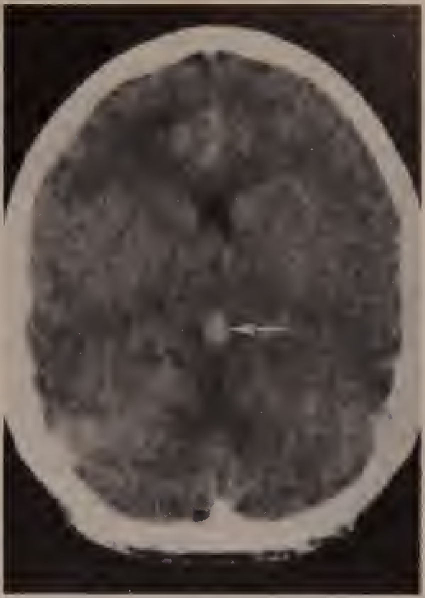

FIGURE 1. A CT scan following injection of intravenous contrast medium on the seventh hospital day that shows discrete hyperdense lesion of blood density in the paramedian midbrain tegmentum.

Discussion. It appears that prolonged survival is possible following severe trauma to midbrain structures even in the presence of a documented hemorrhage. In our patient, the signs of bilateral oculomotor dysfunction and intermittent decerebration were present from the outset. In addition, the discrepancy between the marked midbrain dysfunction and the early recovery of spontaneous purposeful movement and the ability to follow commands localized the brunt of the injury to the brainstem. This discrepancy persisted during recovery.

It is difficult to assess whether the hypertension our patient experienced was a result of, or a contributory cause of, the midbrain hemorrhage. The fact that the oculomotor findings preceded the onset of the hypertension by several days and showed no clinical worsening at the time the hypertension was identified argues against the hemorrhage being solely due to hypertension. Hypertension is a frequent clinical correlate of primary midbrain hemorrhage.[2] It is possible, however, that the hypertension resulted in the extension of smaller hemorrhages, below resolution by CT scan, in an area of recent contusion. It seems that our patient's initial presentation, clinical course, and CT findings are most consistent with a primary brainstem contusion with delayed hemorrhage.

Access to CT scans with ever-improving resolution may help elucidate the sequential effects of trauma to brainstem structures. Severe head trauma can injure the brainstem by either a primary or secondary mechanism. In primary injury, the initial impact causes displacement of supratentorial structures relative to the brainstem or actual lateral or anterior displacement of the upper brainstem against the edge of the tentorium or the clivus, respectively.[2] This results in petechial hemorrhage (contusion) or, less commonly, larger extravasation of blood. In secondary injury to the brainstem, increased intracranial pressure in the supratentorial compartment causes herniation, compression or distortion of the brainstem. This results in the paramedian hemorrhage of the midbrain and upper pons described by Duret.[3] In addition to distortion of the brainstem, disruption of vascular structures, particularly the penetrating arterioles, and venous stasis are believed to play a role in the pathogenesis of these lesions.[1] Most of the brainstem injuries described above are fatal, and hence our knowledge of pathogenic mechanisms is based primarily on postmortem neuropathologic studies. The present case clarifies our understanding of the pathogenic mechanism in a boy with traumatic brainstem hemorrhage and documents his recovery following nonsurgical conservative treatment.

VIJAYA L. ATLURU, MD
Assistant Professor
Department of Pediatric Neurology
SUNY at Stony Brook
Nassau County Medical Center
East Meadow, NY 11554

LEON EPSTEIN, MD
Assistant Professor
Department of Neurosciences
University of Medicine and Dentistry
Newark, NJ

ALBERT ZILKA, MD
Professor
Department of Pediatrics and Radiology
SUNY at Stony Brook
Nassau County Medical Center
East Meadow, NY 11554

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Paraparesis due to licorice-induced hypokalemia

TO THE EDITOR: Hypokalemic myopathy usually produces generalized muscle weakness, sparing cranial innervated muscles.[1,2] An unusual case in which progressive weakness restricted to the legs was due to hypokalemia resulting from chronic licorice ingestion is reported below.

Case Report. A 54-year-old man with a history of diet-controlled diabetes mellitus and long-standing hypertension, controlled by propranolol hydrochloride, 40 mg and hydrochlorothiazide, 25 mg three times a day, was hospitalized for progressive paraparesis of 5 days duration. He denied weakness of arms, trunk or bulbar muscles, sensory or sphincter disturbances, pain, headaches, recent trauma or viral infection, dark urine, compulsive water drinking, alcoholism or history of muscle weakness. His general physical examination was unremarkable. The only abnormality on neurologic examination was symmetrical weakness restricted to the legs with proximal muscles more affected than distal muscles. Deep tendon reflexes (DTR) were diminished in the knees and absent in the ankles with downgoing plantar response. Sensory examination and spinal mechanical testing were normal. The diagnosis on admission was infective polyradiculoneuropathy versus myelopathy.

Initial lab data revealed serum potassium, 1.7 mEq/L; sodium, 146 mEq/L; CO_2, 35 mEq/L; chloride, 93 mEq/L; BUN, 16 mg/dL; glucose, 190 mg/dL, creatine kinase (CK), 623 units/L; and lactate dehydrogenase, 280 U/L. Complete blood count, sedimentation rate, and urine analysis, including urine electrolytes, were normal, with a normal upper limit of urine potassium. An electrocardiogram showed changes consistent with hypokalemia. The patient was started on oral and intravenous potassium supplementation, and the diuretic was discontinued. Within four hours he reported marked improvement in strength, and after receiving 200 mEq of potassium chloride, he regained full strength with return of normal DTR within 14 hours (serum potassium, 2.3 mEq/L). Further questioning disclosed his habit of eating 50 to 100 g of licorice daily for several years.

Additional diagnostic data revealed normal serum calcium, phosphorus, magnesium, creatine, aldosterone, and thyroid function values, with persistently elevated CK. Lumbar puncture (LP) was normal except for a protein of 126 mg/dL. Electromyography and nerve conduction studies on the second day were normal. The patient refused muscle biopsy and a repeat LP. After six days he was discharged and given a smaller dose of propranolol alone and advised to refrain from eating licorice. He has had no recurrence of weakness.

Discussion. Hypokalemic myopathy due to licorice ingestion has been reported.[2-4] The ammonium salt of glycyrrhizinic acid (the active ingredient in licorice) has been shown to produce retention of sodium, water and chloride and increased excretion of potassium in normal individuals.[5,6] These potentially serious metabolic effects have been demonstrated in those who ingest modest amounts of licorice (100 to 200 g, equivalent to 0.7 to 1.4 g of glycyrrhizinic acid) daily for periods as short as one week.[6]

The patient's personal and family history, very low serum potassium, increased urinary potassium excretion during the attack, elevated muscle enzymes, rapid recovery after potassium supplementation and otherwise negative diagnostic data support the diagnosis of hypokalemic paraparesis due to chronic licorice ingestion along with diuretic therapy. We suggest that hypokalemia should be included in the differential diagnosis of paraparesis. Since the patient's blood pressure was subsequently controlled with a smaller dose of propranolol alone, licorice might have been a significant factor in his hypertension. Patients with hypertension and those on diuretic therapy should be warned of the potential hazards of excessive licorice ingestion.

ROSAMMA JOSEPH, MD
JOHN KELEMEN, MD
Division of Neurology
Nassau County Medical Center
2201 Hempstead Turnpike
East Meadow, NY 11554

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Listening to the voice of the community

TO THE EDITOR: I recently took a course on "The Difficult Patient: Dependency on Prescription Drugs and/or Alcohol."

The course was offered to physicians under the sponsorship of the New York Academy of Medicine and the New York Medical Society. The purposes of the course were to familiarize physicians with chemical dependency and the addictive process, to help them recognize the symptoms of the dependencies, and to increase their knowledge of treatment options, especially of self-help groups. Another important goal was to influence the attitudes of private physicians—to give them a new perspective on their own behavior towards the patient who abuses alcohol or drugs. These goals were achieved through attendance at seminars, open meetings of self-help groups such as Al Anon, Pill-Anon and Alcoholics Anonymous, and a session at a hospital treatment center.

The course was particularly relevant because of the growing evidence that community self-help groups may be more effective than the medical profession in dealing with the alcohol and drug dependent individual. With the lay person as the instructor, it was hoped that this consumer-oriented approach would enhance the physician's effectiveness in the daily practice of medicine and medical education.

Sixty-four physicians completed the course. They came from various specialities including family practice, internal medicine, psychiatry and public health. Based on written and verbal comments of the physicians who attended, the course was an enlightening experience. During these two months I learned more about dependency and mood changing chemicals and the life and death problems involved with their use than I had learned in medical school and my entire professional life. I also earned 23 CME credits in a very enjoyable fashion.

Coming from another country (France), where alcoholism is perhaps the number one public health problem (France has the greatest alcohol consumption per capita in the world), I was amazed that the medical education system in France has not yet fully utilized the resources in the community. I have enjoyed this first-hand exposure to a real-life setting with people I usually see across my desk. Having medical responsibilities in a narcotic rehabilitation center, it has helped me with my daily practice and the way I understand my patient's environment.

There is an enormous amount of knowledge among individuals with addictions. They are the people who know and experience their problem best. Physicians as well as other health professionals should learn more about themselves and their reaction to alcoholism and drug dependency, and they should learn how to identify and refer people with such problems to an appropriate treatment facility.

At a time when public funds are being cut for public health and community programs, it is an important responsibility of the private physician to extend the limited resources available in the community. This course gave recognition to the role the community can play.

Physicians should listen more, not only to patients, but also to the general population. After all, most of the time when a physician is called to a meeting, the only thing he does is talk. By listening to the lay groups in the community, a physician will get a better sense of the needs of the population, so that decisions can be made appropriately.

Alcoholism and the abuse of drugs and other substances continues to be a top priority among the public health problems emerging in the 1980s. To understand fully the interaction of biological and social factors that lead to alcohol and other drug dependency, the medical profession should be more exposed to such continuing education sessions in these fields.

CLAUDE J. AGUILLAUME, MD
Department of Community Medicine
The Mount Sinai Medical Center
One Gustave L. Levy Place
New York, NY 10029

A call for political involvement

TO THE EDITOR: Control of the practice of medicine is drifting out of the hands of physicians and into the hands of legislators and certain special interest groups. This assessment, along with blunt criticism of New York State physicians for abdicating regulatory responsibility was the concensus of the speakers at a two-day political education seminar held in March by the New York Medical Political Action Committee (NYMPAC) in Saratoga Springs.

The speakers—including two state assemblymen—Anthony Seminerio and Robert C. Wertz, Tom Berglund, MD, secretary of the American Medical Political Action Committee (AMPAC), and Milton Rosenberg, MD, executive vice president of the Medical Society of the State of New York (MSSNY)—urged attending physicians to encourage their colleagues to become involved in the political process.

Contrary to what many physicians may believe, political activism is not beneath them. Rather, it is required of them if they are to educate New York State legislators, most of whom have limited knowledge of the health issues on which they vote. Without such efforts on the part of physicians, those groups that are politically active—chiropractors, optometrists, and nurse-practitioners, for example—will do the educating. Needless to say, those groups cannot be depended upon to register the physicians' point of view.

But they do a good job of representing their own views. That is why, for example, optometrists can dispense eyedrops and chiropractors can use x-rays more extensively than was previously permitted. When these issues were before the legislature, optometrists and chiropractors made their voices heard.

A proposed bill would allow chiropractors to order diagnostic procedures. Is there any doubt that many of the 2,500 New York chiropractors will once again contact their legislators? Another bill, not yet acted on by the full legislature, would allow nurses to diagnose and treat illnesses and to write prescriptions.

Clearly, the longer physicians wait to become involved in the political process, the less influence they will have when bills such as these are being considered. And complaining about the effects of these bills after the fact does little good.

At the Saratoga Springs seminar, Dr Rosenberg stated his belief that all too many MSSNY members appear to have taken a simplistic approach to politics and have been apathetic when it comes to supporting legislation they favor. "They think that merely because a legislative issue is meritorious. . .it's going to get passed," he said. "They believe that the Medical Society can make things happen by snapping its fingers. It doesn't happen that way." Dr Rosenberg also pointed out that defeated bills that physicians oppose can be, and often are, reintroduced into the legislature.

Physicians' vigilance and activism will be supported by the resources of MSSNY and NYMPAC, which have gathered together people who are very knowledgeable in the medical issues facing legislators. MSSNY has produced position papers and white papers that are available to physicians that want to get involved. In addition, the executive vice president is now a registered lobbyist, making him a more effective ally in the battles facing NYMPAC. As one strategy to win those battles, physicians must gather the funds necessary to help support the campaigns of their political allies. Yet spending funds on campaign contributions, NYMPAC offices, and staff is only half the battle. It does little good to pay a lobbyist a salary and send him off to Albany if the medical profession does not support him. The lobbyists' words must be echoed by phone calls and reinforced by letters from physicians. Legislators must be made to realize that physicians, too, are constituents—and voters—who have valuable opinions on health issues.

The physician's own practice is another conduit to the political arena. Physicians should discuss pending health and medical legislation with their patients, and let their patients know where they stand on the issues, and why. NYMPAC can provide the background information needed to present an intelligent, cogent opinion. Thus, good rapport with patients can be translated into support for the issues physicians stand for, such as good medicine practiced by competent, qualified professionals—and by no one else.

STANLEY J. GRANT
New York Medical Political
Action Committee
Medical Society of New York State
420 Lakeville Road
Lake Success, NY 11042

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MENTAL TESTS OF AUTOMOBILE DRIVERS

In view of the tragic rise in automobile fatalities, medical and psychiatric tests of applicants for driving licenses and mandatory physical and psychiatric tests of licensed drivers at periodic intervals were advocated by Dr. David Kaliski, chairman of the coordination committee, Medical Societies of the Metropolitan Counties, at the Eastern Conference of Motor Vehicle Administrators in New York.

He advocated the testing of drivers every five years up to the age of 55 or 60 and every year thereafter.

Dr. Irving Straus, connected with the New York State Bureau of Motor Vehicles, while questioning the practicability of universal physical and mental tests of drivers, endorsed Dr. Kaliski's position.

(*NY State J Med* 1935; 35:1158)

An analysis of the HDFP trial

Evidence of adverse effects of antihypertensive treatment on white women with moderate and severe hypertension

PETER L. SCHNALL, MD, MICHAEL H. ALDERMAN, MD, ROCHELLE KERN, PHD

ABSTRACT Results of the Hypertension, Detection and Follow-up Program (HDFP) published in 1979 included the suggestion that systematic and effective management of hypertension benefited all individuals with high blood pressure. An analysis of these results reveals, however, that among white women aged 30 to 69 with entry diastolic blood pressure (DBP) ≥105 mm Hg, the "stepped-care" approach was associated with a mortality of 168 percent in excess of the control group ($P = 0.007$ level, $Z = 2.46$). The mortality rate in white men in the stepped-care group with entry DBP >115 mm Hg was 35 percent higher compared to controls. On the other hand, black men and women in the stepped-care group with DBP ≥105 mm Hg had a lower mortality rate compared to the control group. These data suggest that a standard therapeutic regimen may be detrimental when applied to all persons who are identified as having hypertension only by their blood pressure.

(NY State J Med 1984; 84:299-301)

INTRODUCTION

Some aspects of the management of patients with high blood pressure remain controversial despite the mass of data accumulated from extensive clinical trials.[1-8] The findings and conclusions of these trials are being reevaluated on the basis of additional analyses of existing data as well as the gathering of new data. The Hypertension, Detection and Follow-up Program (HDFP) was sponsored by the National Institutes of Health and conducted over a five-year period.[9] Among the trial's chief aims was the assessment of whether the findings of the Veterans Administration Cooperative Group Study (VACGS)[10-12] could be generalized to a heterogeneous, community population. The VACGS involved a selected hospital population of men, most of whom had advanced hypertensive or coronary heart disease, or both. In this paper we present the results of a re-analysis of previously published HDFP data[13] that revealed an association between "stepped care" treatment and increased mortality among white women aged 30 to 69 with moderate or severe hypertension (entry DBP ≥105 mm Hg). We discuss the implications of these findings for the treatment of hypertension in community populations.

HDFP Research Design and Findings. The HDFP was a community-based, randomized controlled trial involving 10,940 persons with hypertension (DBP >90 mm Hg) in 14 communities throughout the United States.[9] Following an initial screening and evaluation, the study sample was stratified by blood pressure level—mild hypertension (DBP 90 to 104 mm Hg) being stratum I (N = 7,825); moderate hypertension (DBP 105 to 114 mm Hg) being stratum II (N = 2,052); and severe hypertension (DBP >115 mm Hg) being stratum III (N = 1,063)—and then assigned randomly (by stratum) to one of two groups: referred care (RC) defined by the HDFP as the control group, or stepped care (SC). Those in the RC group were referred for treatment to their regular source(s) of health care. The SC patients (the experimental group) were offered "systematic, controlled antihypertensive treatment" at one of 14 HDFP health centers.[9] Drug treatment was administered to SC patients according to a stepwise protocol that called for the progressive addition of medication to an individual patient's regimen until his or her blood pressure was brought down to a specified goal level. Two features of the HDFP study design bear notice: (1) the absence of an untreated control group, and (2) the fact that the clinical intervention in the experimental group involved the simultaneous variation of both drug treatment and organization of medical care services.[1,7,8]

The HDFP Cooperative Group has reported that among those in stratum I (with DBP 90 to 104 mm Hg), the SC (as compared with RC) group showed a decrease in all-cause and cardiovascular mortality (including deaths due to stroke).[14-17] Within both strata II and III, the SC group had lower five-year death rates than did the RC group, although this difference was less than in stratum I and was not statistically significant.[15]

METHODS AND RESULTS

In examining the data reported by the HDFP Cooperative Group,

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From the Divisions of Epidemiology (Dr Schnall) and Socio-medical Sciences (Dr Kern), Columbia University School of Public Health, New York, and the Departments of Medicine and Public Health, Cornell University Medical College (Dr Alderman), New York, NY.

Address correspondence to Dr Schnall, NIH-HBLI Post Doctoral Fellow, Division of Epidemiology, Columbia University School of Public Health, 100 Haven Ave, 30th floor, New York, NY 10032.

TABLE I. HDFP Five-Year Mortality for White Women with DBP >105 mm Hg*

DBP at Entry (mm Hg)	Sample Size (no.)		Deaths (no.)		Proportion of Deaths		% Change SC vs RC	Relative Risk	Probability SC vs RC
	SC	RC	SC	RC	SC	RC			
105-114	203	183	15	6	15/203 =0.074	6/183 =0.033	+124	2.2	Z = 1.54 *P* = 0.062
115+	69	51	10	2	10/69 =0.145	2/51 =0.039	+272	3.7	Z = 1.61 *P* = 0.054
Combined DBP > 105	272	234	25	8	25/272 =0.0919	8/234 =0.0342	+168	2.7	Z = 2.46 *P* = 0.007

* Adapted from Kass[13]

we found that among white women assigned to the experimental treatment groups (SC) in both strata II and III (white women who entered with DBPs ≥105 mm Hg) the mortality rate was higher than that in the comparable controls: an excess of 124% in stratum II and 272% in stratum III (see Table I).[13] The combined group finding for white women with DBP >105 mm Hg is statistically significant at the 0.007 level (Z = 2.46). White men in the SC group with entry DBP >115 mm Hg (stratum III) also experienced an excess mortality rate of 35% compared to their RC counterparts, although this is not a statistically significant difference. On the other hand, among both black men and black women assigned to the SC groups in strata II and III, there was a lower all-cause mortality rate than among comparable RC groups.

These findings, which have been reported in the literature but not previously discussed, indicate that the experimental stepped-care treatment (SC) of white women whose initial diastolic blood pressure equalled or exceeded 105 mm Hg was associated with an increased all-cause mortality rate and presumably an increased cardiovascular mortality rate. This excess mortality occurred within the group (SC white women) in which the lowest final blood pressure level was achieved and which contained the highest percentage of subjects whose blood pressure had reached goal levels of any of the subgroups. In addition, the mortality rate of white women with DBP >115 mm Hg in the SC group was higher than that of RC or SC white men and black women with comparable blood pressures. The only blood pressure-defined group with a higher mortality rate was the RC black men.[13]

That antihypertensive chemotherapy would have an inconsistent impact on different groups defined by demographic or clinical characteristics is consistent with what might have been expected from evidence of the natural history of hypertension. For example, analysis of the Framingham data reveals that only two of 100 treated women would be expected to benefit in terms of morbidity or mortality or both, even if a sustained reduction of systolic blood pressure from 165 to 135 mm Hg were maintained for 30 years.[18] It should be noted that this potential benefit is predicated on the assumption that the medications used to reduce blood pressure would, in themselves, be harmless.

These HDFP data do not merely reveal an absence of benefit from treatment. Rather, among white women with a moderate (DBP 105 to 114 mm Hg) or severe elevation of blood pressure (DBP >115 mm Hg), there was a higher mortality rate among those who received SC treatment. Given the small probability of this finding ($P = 0.007$), it is unlikely to have occurred by chance alone. It is also unlikely that the two groups of women (SC versus RC) were significantly different from each other initially since randomization of subjects was employed in the HDFP study design, and at baseline the overall SC and RC groups (all three blood pressure groups combined) were virtually identical.[16]

The magnitude of the difference in death rates between SC and RC white women with DBP >115 mm Hg adds to the impact of the statistical finding. In the HDFP trial the SC subgroup of white women with DBP >115 mm Hg included only 69 subjects of whom 10 died. The control group (RC) had 51 subjects who contributed two deaths. To put this in perspective, in the VACGS trial of patients with DBP 115 to 129 mm Hg, 73 subjects were in the experimental group and 70 subjects in the control group. In that study, there were no deaths and no Class A events in the experimental group (Class A events were new hypertensive complications for which antihypertensive therapy was required; for example, the development of grade III or IV retinopathy) whereas in the control group there were four deaths and 10 Class A events. The difference in event rates was considered sufficient to end the trial with the conclusion that antihypertensive treatment was beneficial.[10] Thus, in these two trials the magnitude of the impact of the intervention is similar, but in opposite directions.

DISCUSSION

This unexpected excess of mortality among white women in the SC group cannot be explained by the data published to date. It would be helpful to know the causes of death among these women, their specific blood pressure courses, their drug experience during treatment as well as center by center experience. Even this information, however, may not explain these results since the design of the HDFP had no untreated control group and involved a treatment intervention in which both drugs and the organization of health services were varied simultaneously.

Two explanations can be proposed: (1) the magnitude of the blood pressure decline was itself detrimental, or (2) the medications prescribed carried a risk that exceeded the benefit of reduced blood pressure. Support exists for both of these hypotheses. In a Norwegian study those with the greatest fall in blood pressure were most likely to experience a cardiac catastrophe.[19] In Australian, Norwegian and United States Public Health Service studies, cardiac mortality was greater in treated than in untreated subjects.[19-21] Additional evidence about the adverse consequences of antihypertensive medication comes from the recently published findings of the Multiple Risk Factor Intervention Trial (MRFIT).[22] The SI subjects (the experimental group) who had hypertension and an abnormal EKG at baseline experienced a 65% increase in coronary heart disease deaths versus the comparable UC group (the control group). Also of concern was that the SI subjects with the lowest diastolic blood pressure (90 to 94 DBP) experienced the greatest relative increase in mortality—17 deaths in the SI group compared to 12 in the UC group. These findings reinforce concerns about a standardized approach to antihypertensive drug treatment for all persons identified only by a certain level of blood pressure.

Clearly, all the hazards of antihypertensive drug therapy are not known. It has been demonstrated that diuretic-induced hypokalemia is associated with increased ventricular arrythmia.[23] The short-term findings of impotence (in men) and peripheral vascular disease have been well documented.[24,25] By contrast, the long-term implications of even mild hyperuricemia, hyperglycemia, and hypokalemia are poorly understood.[26] The HDFP data lend credence to the concern that drug therapy may sometimes produce harm that outweighs its benefit in the treatment of a condition, such as hypertension, in which the inherent risk of the disease is small with an uneven distribution.

Another possible explanation—that community care produced an improvement in the mortality rate by the use of other antihypertensive medications (for example, beta adrenergic agents)—seems unlikely based on the finding that in SC black men and women with moderate and severe elevations of blood pressure, all-cause mortality was lower than in matched RC groups.

Finally, these findings may be explained by chance variations among the subgroups. It is well known that making multiple comparisons increases the likelihood of finding, due to chance alone, that one or more subgroups differ substantially in their outcome from the overall study group results.[27] In assessing the possibility of a chance finding, it should be noted that the results we report are based on the testing of a conservative null hypothesis, that there is *no difference* in outcome between SC and RC in white women with moderate or severe hypertension. On the other hand, we might expect that white women with moderate or severe hypertension could be expected to do significantly *better* in SC than in RC. Clearly, the use of this alternative null hypothesis would have made the probability of the observed results even smaller (produced a larger Z score) and, therefore, would have made the observed results very unlikely to have occurred by chance. Unfortunately, no statistical test can itself resolve the issue of whether these findings are significant or due to chance. Rather, the findings of markedly increased mortality in the experimental SC group among white women with entry DBP >105 mm Hg compared to the RC group must be examined in the context of our expectations of antihypertensive drug treatment effects. Thus, it is the totally unexpected nature of the findings, their magnitude, and the clinical and social significance of their implications that leads us to conclude that they should be taken seriously.

Aggregation of population data in clinical trials may mask important differences within groups, including the presence of negative outcomes for particular subgroups. It seems possible that a thorough examination of results from the HDFP and other clinical trials of antihypertensive drug therapy using social class, age, race, and sex (separately and together) may reveal other subgroups at increased risk from treatment with antihypertensive drugs.

We do not interpret these new findings as conclusive evidence for or against antihypertensive treatment of white women with moderate and severe hypertension, particularly in light of the known limitations of subgroup analysis. Instead, they argue for increased efforts to identify more precisely those individuals and subgroups at highest risk from elevations of blood pressure, as well as those at increased risk from treatment with medications. These data strengthen the view that a scientific basis for a standardized approach to the management of population groups defined exclusively by level of blood pressure does not exist.

Acknowledgment. We are indebted to Dr Steve Ng for his critical review of the manuscript and statistics.

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Complications in fetal macrosomia

NATHAN DOR, MD, HERBERT MOSBERG, MD, WILHELM STERN, MD, NASEEM JAGANI, MD,
HAROLD SCHULMAN, MD

ABSTRACT A three-year review of 8,445 consecutive deliveries showed 441 (5.2%) babies weighing more than 4,000 grams (8.8 lb) and defined as LGA—large for gestational age. This population was analyzed for prenatal complications, mode of delivery and course of labor. Our findings showed that over half of the infants were in the 4,000 to 4,200 grams category. The prevalence rate of diabetes in the mothers of LGA babies was 4 times more frequent (6.8%) and the rate of cesarean section (18.3%) was twice as frequent as found in the mothers of non-LGA babies. The prevalence of shoulder dystocia in the infants increased as the length of the second stage of labor increased. Shoulder dystocia occurred in 17 babies in the LGA group (3.8%) whereas overall prevalence of shoulder dystocia in the non-LGA group was 0.3%.

(NY State J Med 1984; 84:302–305)

INTRODUCTION

Data collected during a three-year experience in a large municipal hospital service showed that there is increased morbidity with LGA (large for gestational age) babies.[1,2] This prompted a review of our data to search for factors associated with shoulder dystocia, a major factor contributing to the increased morbidity in the LGA baby. Neonates that weighed more than 4,000 g were reviewed from an obstetrical point of view to identify the risk factors for labor and delivery. This study revealed that random antepartum ultrasound was of little benefit. However, it is possible that wider use of various ultrasound parameters (transthoracic diameter, abdominal circumference, total intrauterine volume) in addition to biparietal diameter in a serial manner will be more predictive of fetal size. Increased awareness by physicians of the many components associated with shoulder dystocia is important for deciding on appropriate care.

PATIENTS AND METHODS

Between July 1978 and June 1981 8,445 babies were delivered at North Central Bronx-Montefiore Hospital Medical Center in the Bronx. Four hundred forty-one babies were found to weigh more than 4,000 g and were designated as large for gestational age (LGA). In this group we found 17 cases of shoulder dystocia.

The prevalence of shoulder dystocia was compared between the groups weighing over and under 4,000 g. Shoulder dystocia was defined as great difficulty in delivering the shoulders after the head was delivered and pulled back tightly against the perineum.[3] The total group of mothers of LGA babies was evaluated in terms of maternal age, parity, prenatal complication, course of labor and mode of delivery. Newborns were evaluated by weight distribution and Apgar scores. A statistical comparison of the above parameters, using a Chi squared test, was done relative to infants weighing less than 4,000 g.

RESULTS

Maternal age and parity (Table IA,B). The maternal age ranged from 15½ years to 45 years. The distribution of patients by age is shown in five-year intervals, with the largest group of patients (34%) falling between the ages of 20 and 24 years; 79% of the patients were between 20 and 34 years of age. 29.4% of the babies were born to primigravida women and 70.6% were born to multiparous patients. Of the non-LGA babies, 38% were born to primigravida women and 62% to multiparous patients.

Ultrasound. Seventy-five patients of the total LGA group (17%) had at least one sonogram done, mainly to assess the biparietal diameter. The sonograms were performed at various periods during the pregnancies.

Fetal weight (Fig 1). The majority of the infants, 246 or 55.7% of the total LGA group, were in the range of 4,000 to 4,200 g. This group accounted for 2.9% of the total number of deliveries between 1978 to 1981 and 3.2% of all term deliveries. The prevalence of all babies weighing more than 4,000 g was 5.2%. Sixty-six babies weighed more than 4,500 g (10 lb).

Prenatal complications (Table II). Thirty mothers had diabetes. The total prevalence of diabetes in mothers of the LGA group was 6.8% including class A and B according to the White classification.[4] Nineteen had class A gestational diabetes—4.3% of the total patients, and 11 had class B—2.5% of the total. The overall prevalence of diabetes in our general obstetrical population is 1.7%. Twelve patients developed pregnancy-induced hypertension, an incidence of 2.7% which is lower than the common rate for preeclampsia (9.8%) in our general population.

Presentation. There were 13 breech presentations giving a prevalence rate of 2.9%. The prevalence rate of breech in our general obstetrical population was 3.4%. Four patients with breech presentation had vaginal deliveries and nine patients underwent cesarean section.

Indications for cesarean section (Table III). Of the LGA group, 18.3% underwent cesarean sections, a figure almost double that of our general obstetrical population. The primary cesarean section rate for infants in the LGA group was 14.2%. Forty-six percent of the sections were done for failure to progress. Six sections (7.5%) were done because the estimated fetal weight was greater than 4,000 g. Comparing the cesarean section rate in the LGA group to the normal population showed a statistically significant higher rate of cesarean section in the LGA group. ($\chi^2 = 7.2$, $P < 0.001$). The probability of a cesarean section seemed to rise as the weight of the baby increased (Fig 2). There was a significantly greater frequency of cesarean sections in mothers of babies larger than 4,800 g (38% versus 11%, $\chi^2 = 4.41$, $0.01 < P < 0.05$).

Apgar score. A comparison of the Apgar scores of the non-shoulder dystocia versus shoulder dystocia cases revealed no statistically significant differences.

Course of labor (Fig 3,4). For the total group the first stage of labor was more than 10 hours for 35% of the patients. In the shoulder

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From the Department of Obstetrics and Gynecology (Drs Dor and Mosberg), Maimonides Medical Center, the Department of Radiology (Dr Stern), North Central Bronx-Montefiore Medical Center, Albert Einstein College of Medicine, and the Department of Obstetrics and Gynecology (Drs Jagani and Schulman), Bronx Municipal Hospital Center, Albert Einstein College of Medicine, New York.

Address correspondence to Dr Dor, Chief, Fetal & Maternal Medicine, Department of Obstetrics and Gynecology, Maimonides Medical Center, 4802 10th Ave, Brooklyn, NY 11219.

Table IA. Distribution of Patients According to Age in LGA Group

Age (yrs)	15	15–19	20–24	25–29	30–34	35–39	40–44	45
No. of patients	0	58	150	110	88	22	13	0
Percentage of patients	0	13	34	25	20	5	3	0

Table IB. Distribution of Babies According to Maternal Parity in LGA Group

Parity	0	1	2	3	4	5	6	7	8
No. of babies	130	146	88	34	21	11	9	1	1
Percentage of babies	29.4	33.2	20	7.6	4.8	2.6	2.0	0.2	0.2

Table II. Prenatal Complications

Complication	Number of Patients	Percentage of Total Patients in LGA Group
Class A diabetes mellitus	19	4.3
Class B diabetes mellitus	11	2.5
Chronic hypertension	19	4.3
Pregnancy-induced hypertension	12	2.7
Hypothyroidism	2	0.5

Table III. Indications for Cesarean Sections

Indications	Number of Patients	Percentage of Patients
Failure to progress	37	46
Repeat cesarean section	18	22
Fetal distress	14	17
Estimated large fetus (>4,000 g)	6	7.5
Incomplete breech	6	7.5
Total	81	100

Table IV. Weight Distribution of Babies with Shoulder Dystocia

Weight	Number	Percentage Shoulder Dystocia	Shoulder Dystocia as a Percentage of the Total Group
<4,000	28	0	0.3
4,000–4,200	6	35	1.36
4,201–4,400	5	29	1.13
4,401–4,600	3	18	0.68
4,601–4,800	1	6	0.23
4,801–5,000	1	6	0.23
>5,000	1	6	0.23
	45	100	3.86

dystocia group 41% of the patients had a first stage of more than 10 hours. This difference was not statistically significant.

The prevalence of shoulder dystocia increased as the second stage of labor became prolonged (greater than two hours). 13.3% of the total LGA group developed shoulder dystocia when the second stage was beyond 70 minutes. When the second stage was less than 70 minutes, the prevalence of shoulder dystocia in the LGA group was 3.5%, not statistically significant (Fisher's exact test, $P > 0.5$).

The prevalence of shoulder dystocia in the normal obstetrical population was 0.35%. Therefore, in our study shoulder dystocia was 10 times more common when the infant's weight exceeded 4,000 g ($P < 0.0001$, Table IV).

DISCUSSION

Over 100,000 large for gestational age infants are born each year in the United States.[1,5,6] These babies are prone to increased perinatal morbidity and mortality, mainly because of a higher incidence of shoulder dystocia especially in training institutions where the house staff might lack the experience to treat this situation. The relative lack of awareness of this entity and its low frequency of occurrence, especially in private practice, led us to explore some of the problems that might be associated with it.

The frequency of fetal macrosomia varies throughout the world. In the Baltimore area the prevalence was found to be 1.1%. In Denver, 5,000 feet above sea level, the prevalence was 0.3% and above 9,000 feet the prevalence was 0%.[6] In Harlem, NY the prevalence was 0.6%.[7]

In our series, 5.2% of the newborn infants weighed more than 4,000 g and 0.7% weighed more than 4,500 g, in a population composed of 35% black patients and 65% white patients.

We found certain features to be more common in mothers of macrosomic babies, including multiparity, diabetes mellitus, prolonged second stage of labor and a higher prevalence of shoulder dystocia and cesarean sections. Sack noted the high frequency of multiparity among mothers of large infants.[1] This frequency may go as high as 90.2%.[1,8] Our data shows a multiparity rate of 331 patients, 70.6%. We did not note a particular age group in which macrosomia was more prevalent. The total age distribution was from 15½ to 44 years of age.

In most series diabetes is associated with fetal macrosomia.[1,5,7–12] The relationship of large babies at birth to the future development of diabetes is equally, if not more im-

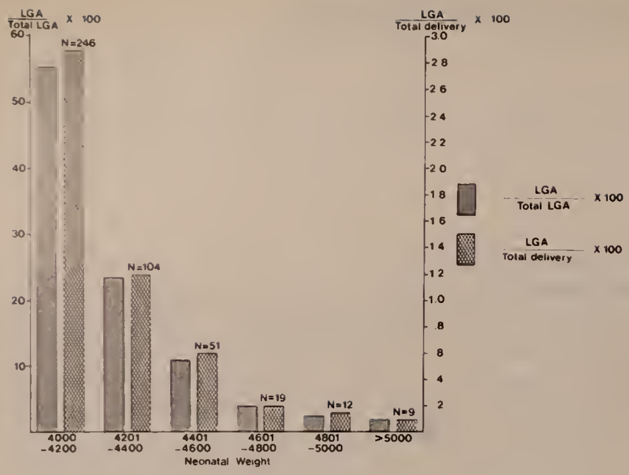

FIGURE 1. Distribution of babies as a function of birth weight.

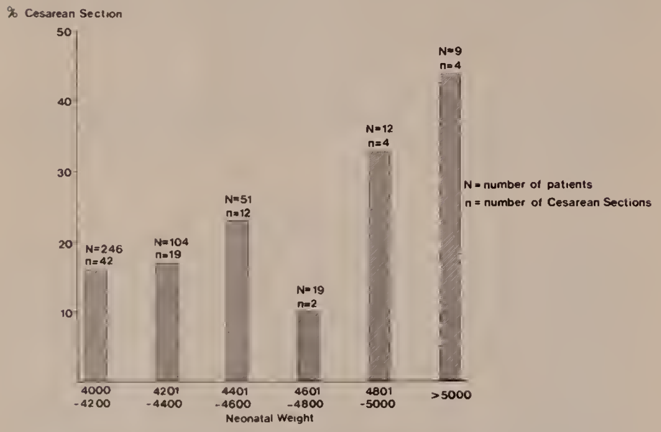

FIGURE 2. Incidence of cesarean section according to birth weight.

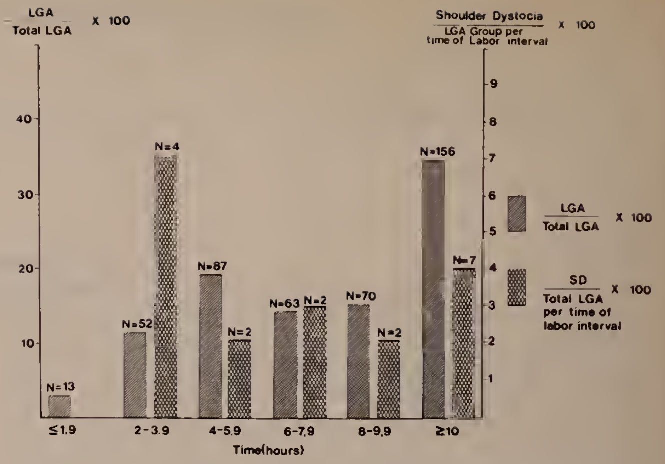

FIGURE 3. Duration of labor in the first stage in the shoulder dystocia group. The shoulder dystocia group is expressed as a percentage in relation to the LGA group for each time interval.

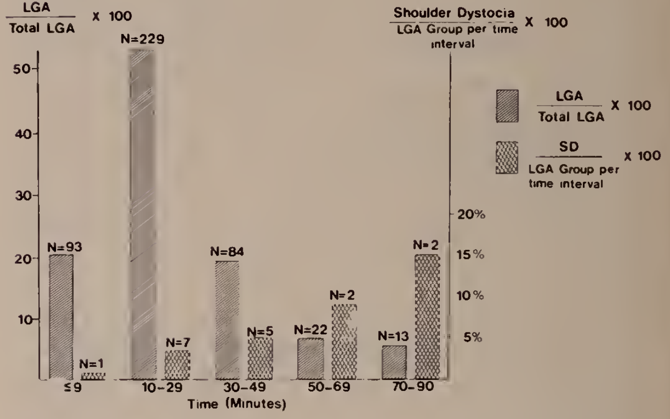

FIGURE 4. Duration of labor in the second stage in the shoulder dystocia group. The shoulder dystocia group is expressed as a percentage in relation to the LGA group for each time interval.

portant. Posner[7] found a 10-fold increase in diabetes in the macrosomic group compared to the general obstetric population, and similar findings were noted by others.[1,2,7,9,13] Our data is in general agreement with these studies: the prevalence of diabetes in our LGA group was 6.8% compared to 1.7% in our general obstetric population. Pregnancy-induced hypertension has been mentioned as a condition that rises in frequency in association with large babies.[7,13] In some reviews the prevalence was 3 to 4 times greater than in the general population.[14] Our data did not reveal any significant increase in this disorder, and similar findings have been noted.[5,8]

Our data shows that the size of the fetus does not have a significant effect on the length of the first stage of labor. However, the second stage might be prolonged if the baby is large. This finding has prognostic importance in regard to the development of shoulder dystocia.[10] In our study the prevalence of shoulder dystocia in the LGA group increased from 1% when the second stage was less than nine minutes to 13.3% when the second stage was greater than 70 minutes. The LGA group in the weight range of 4,400 to 4,600 g accounted for the largest percentage of shoulder dystocia cases.

Most investigators consider shoulder dystocia as a recognized complication in the LGA fetus and have reported prevalence rates of from 3% to 18%.[2,15] Although the prevalence of shoulder dystocia in the general obstetrical population is 0.15% to 0.60%, in the LGA baby it is markedly higher. The total prevalence of shoulder dystocia in our LGA group was 3.8%, and this finding is in agreement with other studies. All of the shoulder dystocia cases were associated with non-operative spontaneous vaginal deliveries. Benedetti and Gabbe[10] have shown that prolonged second stage and midpelvic operative delivery can be dangerous to the fetus.

From previous reports in the literature and from our findings we suggest the following as factors associated with shoulder dystocia: multiparity, post datism, previous large for gestational age fetus, maternal diabetes, excessive weight gain in pregnancy, palpable large fetus, advanced maternal age, fundal height greater than 40 cm, and poor progress in second stage of labor.

We undertook a retrospective review of the antepartum and intrapartum problems that can arise with a large fetus. Suspicion of shoulder dystocia requires an acute awareness of the many factors involved as a guide to the diagnosis and management of the condition. An experienced obstetrician and anesthesiologist should be available if vaginal delivery of an LGA baby is anticipated. Cesarean section should be performed when the infant is estimated to weigh more than 4,000 g.

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FROM THE LIBRARY

A WORD TO OUR CONTRIBUTORS

There is nothing more congenial to the editor than the ability and power to please his contributors. It would be delightful for him and for all if every man could have his paper printed "right away." Unfortunately the *New York State Journal of Medicine* only appears once a month. It shines for all—all good doctors at least who are members of their County Society—perhaps by reflected light for others also. Its pages are not elastic, however, and it does sometimes add a wrinkle to the brow of care when gentlemen get excited because their papers do not appear at once. Softly all of you please. Hearken to the policy of the editor. Each of the succeeding numbers of the *Journal* will be devoted one-half to papers from District Branches and County Societies, one-half to papers from the annual meeting. In this way the editor hopes to be fair to all and escape more or less reproachful correspondence.

At the same time, do not deny him the privilege of selection. A particular paper may be timely and require early publication, while others sometimes acquire flavor and strength like old wine, by keeping. So also juxtaposition often adds to the value of a paper. Therefore, friends, be patient, if you do not appear in print at once. We are doing the best that can be done under the circumstances and limitations which surround a monthly journal of a limited size.

Editorial
(*NY State J Med* 1910; 10:52.)

Diffuse lymphadenopathy and anasarca in a 65-year-old woman

CASE PRESENTATION

Daniel Cameron, MD (Medical Resident): A 65-year-old bookkeeper was admitted to the Medical Service with complaints of total body swelling for four months and shortness of breath for one week.

The patient had been in good health until one year before admission when she noted a lump above the left clavicle. She was treated for this with oral medications by a physician. However, additional masses in the left side of the neck were noted, and four months before admission progressive swelling of the legs and groin appeared. Two months later the patient was admitted to Beth Israel Medical Center with firm fixed nontender enlargement of lymph nodes in the left cervical, left axillary, left submandibular, and right inguinal areas. The physical examination revealed pitting edema of both lower extremities. Laboratory studies included a WBC count of 6,500/mm^3, hemoglobin of 11.5 g/dL, hematocrit of 35.4%, and normal red blood cell indices. The serum sodium was 135 mEq/L, serum chloride 96 mEq/L, serum potassium 3.3 mEq/L, and serum bicarbonate 29 mEq/L; the serum glucose was 92 mg, blood urea nitrogen 6 mg, serum creatinine 0.9 mg, and serum calcium 8.6 mg/dL. The erythrocyte sedimentation rate was 90 mm/hour. The serum lactic dehydrogenase (LDH) level was elevated (432 U), serum albumin was low (2.8 g), and serum protein electrophoresis confirmed the hypoalbuminemia.

The chest film indicated the presence of bilateral pleural effusions without cardiac enlargement.

A CT scan of the abdomen revealed bilateral pleural effusions, normal appearing liver and spleen, and extensive retroperitoneal lymphadenopathy around the aorta and inferior vena cava, extending into the iliac chains. Surgical biopsy of the left cervical and right inguinal nodes was performed, and the patient was discharged with a clinical impression of suspected lymphoma. The final pathologic report on these biopsies, however, indicated the presence of metastatic cancer, probably a poorly differentiated adenocarcinoma. The patient refused further outpatient therapy.

One week prior to her final admission, the patient noted swelling of the legs, arms, and abdomen, as well as dyspnea, orthopnea, and inability to ambulate.

The medical history was remarkable for a history of cholecystitis and onset of menopause at age 45; the patient denied regular use of medications, alcohol or tobacco.

Physical examination at the time of the patient's final admission revealed a woman in advanced respiratory distress. The blood pressure was 120/80 mm Hg; the pulse rate was 120/min and the respiratory rate 30/min; the temperature was 98.6°F. There were no orthostatic changes in blood pressure or pulse rate. Examination of the head and neck revealed only bilateral cervical adenopathy. The breast examination did not reveal any masses. The lung fields were dull to percussion over the lower half on both sides, with decreased breath sounds. The cardiac examination revealed a regular rhythm, tachycardia of 120/min, an S-3 sound, and no murmurs. Examination of the abdomen revealed anasarca, probable ascites, normal bowel sounds, and no palpable masses. The findings on rectal examination were within normal limits; the stool guaiac test for blood was negative. There was 3+ pitting edema of both upper and lower extremities.

The patient was alert and oriented; the neurologic evaluation did not reveal any abnormalities.

Laboratory studies indicated a WBC count of 15,500/mm^3 with 88% polymorphonuclear leukocytes, 7% band forms, 1% lymphocytes, and 4% monocytes. The hemoglobin was 13.3 g/dL, hematocrit 39.6%, platelets 332,000/mm^3, and the red blood cell indices were normal. The serum sodium was 106 mEq/L, serum chloride 79 mEq/L, serum potassium 5 mEq/L, and bicarbonate 17 mEq/L. The serum glucose was 109 mg/dL, BUN 7 mg/dL, creatinine 0.8 mg/dL, serum calcium 7.9 mg/dL. The prothrombin time was 10.5 sec (control 10.3 sec) and the partial thromboplastin time was 34.2 sec (control 30.1 sec). The EKG revealed a sinus tachycardia of 112/min.

The chest film indicated the presence of bilateral pleural effusions with pulmonary congestion. The arterial blood gas determinations on room air showed a pH of 7.40, P_{CO_2} of 30 mm Hg, P_{O_2} of 37 mm Hg, and an oxygen saturation of 71%. On 40% nasal oxygen therapy, the arterial pH was 7.35, P_{CO_2} 36 mm Hg, P_{O_2} 54 mm Hg, and the oxygen saturation 87%.

The urine was clear and yellow with a pH of 5.0 and a specific gravity of 1.026; it was positive for acetone, but negative for protein, with a trace positive test for blood. Microscopic examination showed only 0 to 2 white blood cells, and 1 to 2 red blood cells/hpf. Urine electrolyte de-

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Based on the clinicopathologic conference (CPC) held at Beth Israel Medical Center, New York, NY, on November 28, 1983.

Moderator: Susan Zeveloff, MD; *Clinical Discussion:* Neal Mittman, MD, Assistant in Medicine, Division of Nephrology; *Radiology Presentation:* Lowell B. Barek, MD, Attending Physician, Department of Radiology, Mount Sinai School of Medicine; *Pathology Presentation:* Roberto Cipolla, MD, Resident in Pathology.

Editor: JOHN T. FLYNN, MD.

Address correspondence to Dr Flynn, Consulting Editor, *New York State Journal of Medicine*, PO Box 5404, 420 Lakeville Rd, Lake Success, NY 11042.

terminations revealed a sodium of 5 mEq, chloride 21 mEq, potassium 44 mEq, creatinine 102 mg, and osmolality 752. The sequential multiple analyzer (SMA) 12/60 indicated an elevated LDH level of 581 IU and a serum albumin of 2.3 g/dL. Thyroid function studies disclosed a low triiodothyronine (T_3) level.

Treatment was begun with intravenous normal saline solution, at 100 mL per eight hours, and total fluid intake was restricted to 500 mL over 24-hour periods. Paracentesis was unsuccessful. On the second hospital day, the central venous pressure was 15.5 mm. After the intravenous administration of 40 mg of furosemide, a diuresis of 1,200 cc of urine resulted over the next eight hours as compared with 360 cc in the preceding eight hours.

On the third hospital day, the patient appeared stuporous and was hypotensive; only 200 cc of urine was passed at eight-hour intervals. The central venous pressure was 14 mm Hg; the serum sodium was 112 mEq, serum chloride 78 mEq, serum potassium 4.9 mEq, and the serum bicarbonate 21 mEq/L. The serum glucose was 104 mg, BUN 17 mg, and the serum creatinine 1.0 mg. The arterial blood gas determination on 70% oxygen revealed a pH of 7.28, P_{CO_2} 46 mm Hg, P_{O_2} 61 mm Hg, and 88% saturation. The patient was placed in a Trendelenberg position and was given intravenous methylprednisolone, 1.0 g and furosemide, 20 mg. She died on the fourth hospital day.

RADIOLOGY PRESENTATION

Lowell B. Barek, MD (Attending Physician, Department of Radiology): The in-hospital chest film obtained two months prior to the final admission showed some posterior mottling. The chest film obtained later in the same hospitalization showed extensive bilateral pleural effusions as well as congested pulmonary vessels.

The CT scan of the chest revealed large bilateral effusions medial to the hemidiaphragms, indicating their location in the chest rather than in the abdominal cavity. More caudad images on the scan showed a small amount of fluid anterior to the left hemidiaphragm, indicating its location in the abdomen. On further caudad, the spleen and liver were clearly outlined, as were the aorta, the vertebral bodies, and the stomach, along with the abdominal fluid. Further inferiorly, there was evidence of soft-tissue densities behind the diaphragmatic crura, representing retrocrural adenopathy. The liver, the upper pole of the left kidney, the stomach, and a portion of the pancreas appeared normal. Lower down, we could see the celiac axis originating from the aorta, the splenic artery, the hepatic artery entering the porta of the liver, the spleen, and the kidneys. Lower still, the superior mesenteric artery was visible, with masses of soft tissue densities surrounding the aorta, which represented lymphadenopathy. The tail of the pancreas, the stomach, the kidneys, the splenic flexure of the colon, and the liver all appeared normal.

As we moved still lower, we could see a density within the gallbladder, either a floating stone or an artifact due to the ascites that surrounded the gallbladder and gave the appearance of a floating gallbladder. It was difficult to be sure which was the more likely here. Still lower, we continued to see the adenopathy; the abdominal aorta was surrounded by a massive accumulation of enlarged retroperitoneal nodes which extended downward to the aortic bifurcation and along the iliac vessels bilaterally. The adenopathy was retroperitoneal and retrocrural and did not involve the mesenteric nodes. The head of the pancreas, the superior mesenteric artery, the superior mesenteric vein, and the tail of the pancreas all appeared normal. The CT scan covered the upper third of the pelvis; no other abnormalities were seen. The bones appeared normal.

CLINICAL DISCUSSION

Neal Mittman, MD (Assistant in Medicine, Division of Nephrology, Beth Israel Medical Center): The patient under discussion was a 65-year-old woman with metastatic malignancy who presented with severe hyponatremia. I will present an evaluation of this particular electrolyte disorder and try to integrate the pathophysiology of this patient's disease process.

The differential diagnosis of hyponatremic disorders is best approached by assessing the extracellular fluid volume in relation to serum osmolality.[1,2] Osmolality is simply the measure of osmotically active solute concentration, particle number irrespective of size or weight. Ions and small molecules, because of their relatively large number, determine osmolality. Under normal circumstances, serum osmolality is determined by the concentration of sodium and its anion, so that serum osmolality is usually slightly higher than twice the serum sodium concentration. In general, hyponatremia implies hypoosmolality. A measure of serum osmolality is not recorded in the protocol of the patient under discussion, but we can estimate the serum osmolality as being twice the serum sodium, plus the serum glucose divided by 18, plus the blood urea nitrogen divided by 2.8. Thus, prior to the initiation of therapy, the calculated serum osmolality was 220 mosm, the normal level being 285 to 295 mosm/kg H_2O; the hypoosmolality was due to the hyponatremia.

The presence of a lower than normal serum sodium concentration does not always imply the presence of hypoosmolality. The serum is 93% fluid by volume; the other 7% consists of fat and protein. Since electrolytes are dissolved in the water compartment of the serum, electrolyte measurements underestimate plasma water concentration by 7%. The patient who has substantial increases in either serum lipids or serum protein concentrations may show an artifactual reduction of the measured serum sodium concentration as the water phase of the plasma is reduced. Thus the concentration of sodium in plasma water could be normal, but the measured concentration could be low. This situation may be suspected when there is a discrepancy between the calculated serum osmolality of the blood and the measured osmolality, since the latter is not influenced by the lipid and protein content. There is no reason to suspect such artifactual hyponatremia in this patient, since the blood chemical determinations did not reflect any increase in serum lipids or proteins. Hyperlipemia may be excluded as a cause of hyponatremia by simple inspection of the serum, which must be grossly lipemic or lactescent for pseudohyponatremia to occur.

A pathophysiologic situation in which hyponatremia is not associated with hypoosmolality occurs when a high concentration of low molecular weight solutes is localized in the extracellular fluid, such as with severe hyperglycemia or with intravenous infusions of large amounts of mannitol. Under these conditions, because of the accumulation of osmoles in the extracellular fluid, water is drawn from the cells and results in a dilution of the serum sodium. We have no evidence of such processes in this patient.

Under most other conditions hyponatremia signifies hypoosmolality. However, this does not imply that a single disease process is responsible for the condition.

Hypoosmolar states are best considered according to the status of the body sodium and water compartments. The first category of hypoosmolar states is hypovolemic hyponatremia in which there is a significant deficit of total body water and an even larger deficit of total body sodium. Clinically there are signs of fluid volume depletion; the sodium losses may be renal or extrarenal. Renal sodium wasting can result from salt-wasting interstitial nephropathy, mineralocorticoid deficiency, or diuretic excess. Extrarenal losses occur through the gastrointestinal tract. In the patient who appears hypovolemic, renal and nonrenal losses are differentiated by measuring the urinary sodium concentration. In extrarenal losses, the urine sodium concentration should be less than 10 mEq/L, reflecting enhanced tubular reabsorption. With renal and adrenal losses, the urine sodium concentration is higher, usually greater than 20 mEq/L.

The second category of hypoosmolar hyponatremia is related to a primary excess of total body water, associated with a normal or nearly normal total body sodium. This mildly hypervolemic hyponatremia is associated with an inapparent, nonedematous expansion of extracellular fluid volume. Such patients have a primary defect in the renal excretion of free water. Excluding patients with renal insufficiency in whom impaired water excretion can result from the reduction in renal mass, there remain those patients in whom water excretion is inadequate despite an intact kidney. The majority of such cases are due to a high antidiuretic hormone effect. A number of pharmacologic agents have been described that impair renal water excretion through the action of antidiuretic hormone, either by stimulating its release or enhancing its action. Our patient was not known to be receiving any medications that have such capacities.

Inappropriate antidiuretic hormone (SIADH) syndrome is manifested by hyponatremia, hypoosmolality, high urinary osmolality, and urinary sodium excretion that reflects sodium intake and is usually greater than 20 mEq/L. The syndrome occurs in three disease categories: pulmonary diseases, central nervous system disorders, and malignancies. This last group includes oat cell carcinoma of the lung and carcinomas of the esophagus, duodenum, colon, pancreas, and ovary.[3] SIADH should be considered in any patient with malignancy and hyponatremia; however, in our patient the low urinary sodium speaks against SIADH, and the diagnosis cannot be made in the presence of an edematous disorder.

Adrenal insufficiency and hypothyroidism must be considered as possible causes of euvolemic hyponatremia. With adrenal failure, mineralocorticoid deficiency is associated with sodium wasting; glucocorticoid deficiency also impairs water excretion due to its permissive effect on maximal water impermeability of the collecting duct or excessive antidiuretic hormone secretion, or both. Hypothyroidism also impairs renal diluting capacity, although the mechanism is uncertain. Postulated mechanisms include a reset osmoreceptor, a relative cortisol deficiency, and antidiuretic hormone excess. In our patient, adrenal insufficiency was unlikely, given the patient's low urinary sodium concentration. The low T3 level recorded in our patient probably reflects a low peripheral conversion of thyroxine (T4) to T3, rather than a true hypothyroidism.

The final category of hyponatremic states is that of hypervolemic hyponatremia—the edematous disorders. In these situations there is a substantial expansion of total body sodium with an even greater expansion of total body water. In these patients, the impairment of water excretion has been attributed to a decrease in the delivery of sodium and water to the distal diluting sites and to nonosmotic release of antidiuretic hormone secondary to ineffective circulating blood volume. One can, therefore, envision avid sodium reabsorption in the proximal renal tubule leading to a low urinary sodium concentration, and high levels of antidiuretic hormone resulting in distal water reabsorption and high urinary osmolality.

During our patient's final admission she presented with anasarca and hypervolemic hyponatremia. The edematous hyponatremias are nephrosis, cirrhosis, and congestive heart failure. Various neoplasms, including carcinomas of the lung, colon, stomach, breast, cervix, ovary, kidney, thyroid and oropharynx have been associated with the nephrotic syndrome. The predominant glomerular lesion is a membranous glomerulopathy, apparently due to the deposition of tumor-associated antigen-antibody complexes in the glomerular capillaries. Despite the hypoalbuminemia and microhematuria, the patient did not have proteinuria. Therefore, it is not reasonable to postulate that she had the nephrotic syndrome. The normal liver function tests and liver enzyme levels, in addition to the normal appearance of the liver and spleen by computerized tomography, make hepatic cirrhosis an unlikely pathophysiologic explanation. The patient was, however, in severe biventricular heart failure at the time of presentation, and the low urinary sodium and the high urinary osmolality are consistent with this. Intrinsic heart failure does not explain her earlier course; the patient had noted generalized edema several months earlier, and salt and water retention in the form of lower extremity edema and bilateral pleural effusions without cardiomegaly were seen two months before the final admission.

Edema can be caused either by increased formation or by decreased removal of interstitial fluids. The former can be induced either by increased capillary hydrostatic pressure or by increased capillary permeability. Removal of interstitial fluid can be decreased either by impaired lymphatic outflow or by diminished plasma oncotic pressure. Plasma volume loss into the interstitial spaces decreases the effective circulating volume and induces the kidney to retain salt and water. All of the conditions that cause edema formation have in common an increased tendency for the renal tubules to reabsorb excessive amounts of sodium and water; this is responsible for the progressive accumulation of edema. The combination of avid sodium and water retention coupled with continued sodium and water intake serves to maintain and worsen the edematous state.

It is likely that the edema formation in this patient was caused by several factors. A state of hyperaldosteronism may be inferred from the serum electrolyte concentrations two months earlier. Diminished plasma oncotic pressure from hypoalbuminemia and impaired lymphatic outflow related to the extensive adenopathy are likely contributors. It is tempting to suggest that there may have been partial vena caval obstruction secondary to the lymphadenopathy. Depending on its location, vena caval obstruction can be associated with diminished cardiac output, hyperaldosteronism, and increased adrenergic activity. Progressive sodium retention and anasarca secondary to vena caval obstruction have been produced in animal models and have been observed in human patients.

The histologic diagnosis of poorly differentiated adenocarcinoma in this patient is suggested by the lymph node biopsy. The histologic distinction between poorly differentiated malignancies can be difficult, especially when the specimen or preparation is inadequate. Therefore I would not exclude an undifferentiated non-Hodgkin's lymphoma.

A year prior to admission the patient noted a lump above the left clavicle. This may have been a Virchow's node, reflecting distant metastases from the tumor in the abdominal cavity that was already present. Pelvic lymphatic drainage is suggested by the pattern of lymphadenopathy. Renal adenocarcinoma drains through the paracaval and pelvic nodes and is a consideration in view of the microhematuria. The CT scan, however, did not reveal any renal masses. Other malignancies of the gastrointestinal tract, including colorectal adenocarcinoma, are possibilities, but a single stool examination was reported to be guaiac negative, and the abdominal CT scan did not suggest a colonic or pancreatic malignancy.

Ovarian carcinoma may be in an advanced stage when first identified. Ascites often accompanies ovarian carcinoma either due to peritoneal extension or to venous obstruction caused by partial torsion of the tumor. The association of hydrothorax and ascites with ovarian neoplasms (including carcinomas)—Meig's syndrome—is not well understood. Lymphatic drainage through the diaphragm is the likely route for ascitic fluid to the chest. In our patient ascites was present at the time of her initial presentation and, therefore, an ovarian carcinoma and malignant Meig's syndrome would tie together the major clinical elements in a single diagnostic entity.

In summary, this patient was a 65-year-old woman with diffuse carcinomatosis, perhaps ovarian in origin, and progressive generalized edema of multifactorial origin. The severe hyponatremia resulted from a defect in free water clearance. I suspect that the terminal event was sepsis, perhaps from a peritoneal source.

Ralph Zalusky, MD (Chief, Division of Hematology-Oncology, Beth Israel Medical Center): There was one attempt at a paracentesis. Would the character of the fluid—an exudate versus a transudate—have influenced your considerations?

Dr Mittman: Of course ascites caused by a malignancy should result in an exudate, whereas an effusion of cardiogenic origin would be expected to be a transudate.

Dr Zalusky: Dr Barek, how useful is the CT scan from the standpoint of determining the presence of gastrointestinal malignancies?

Dr Barek: On occasion, such malignancies may be identified on the CT scan. However, a negative CT scan does not rule out a malignancy.

Dr Zalusky: Examination of the tissue biopsy specimen for surface markers might be helpful in situations in which it is difficult to determine by histologic appearance whether the lesion is a poorly differentiated adenocarcinoma or a lymphoma. Such a differentiation by surface markers would not be indicated when the biopsy specimen can be read unequivocally as adenocarcinoma.

CLINICAL DIAGNOSES

Diffuse lymphatic spread of poorly differentiated adenocarcinoma, probably ovarian in origin, with ascites and malignant Meig's syndrome.

Generalized edema of multifactorial origin associated with congestive heart failure, hypoalbuminemia, secondary hyperaldosteronism, lymphatic obstruction, and possible vena caval obstruction.

Probable terminal sepsis.

PATHOLOGY PRESENTATION

Roberto Cipolla, MD (Resident in Pathology): The lymph node biopsy specimen obtained during the first admission was reported as showing poorly differentiated carcinoma, with anaplastic cells that were unequivocal evidence of metastatic carcinoma (Fig 1).

At autopsy, diffuse edema, adenopathy, and marked ascites were present. On opening the abdomen, over 1,000 cc of clear ascitic fluid was found. The uterus was atrophic; both ovaries were enlarged, especially the left, which measured 7 cm in largest dimension and showed multiple cysts on the surface (Fig 2). The right ovary measured 2 cm in maximum dimension and showed similar multiple cysts on the surface. The cut surface of the left ovary revealed a firm tan-brown solid mass with areas of focal hemorrhage and cyst formation. The histologic appearance of this tumor was identical with that of the lymph node biopsy specimen: large anaplastic cells with hyperchromatic nuclei arranged to form papillary configurations (Fig 3). Psammoma bodies were also seen. These findings are indicative of a primary papillary poorly differentiated carcinoma of the ovary. The right ovary showed the same histologic picture, so that the

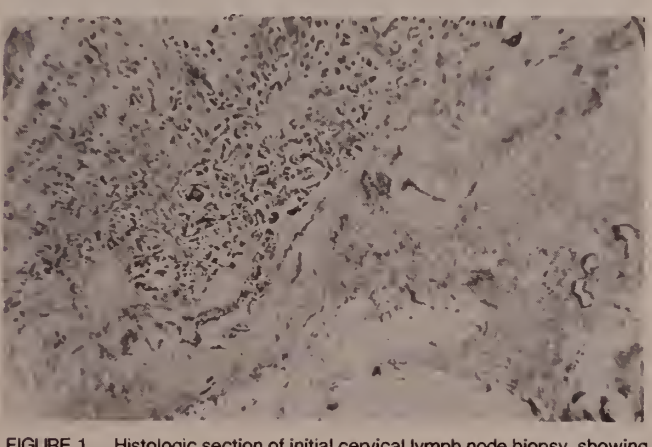
FIGURE 1. Histologic section of initial cervical lymph node biopsy, showing extensive poorly differentiated carcinoma. (Hematoxylin and eosin stain, original magnification ×25.)

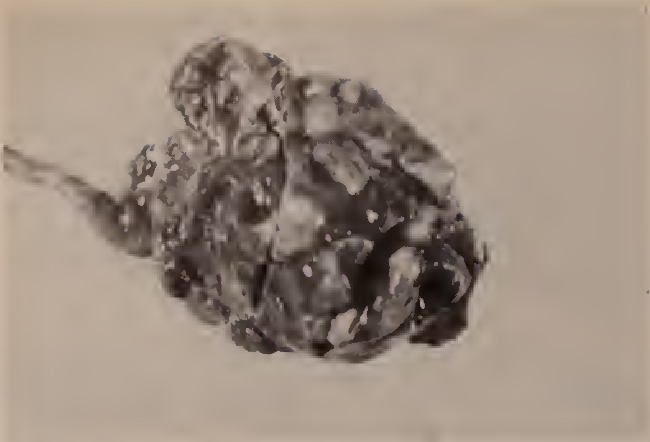

FIGURE 2. Left ovary completely replaced by large partially cystic and partially solid tumor mass.

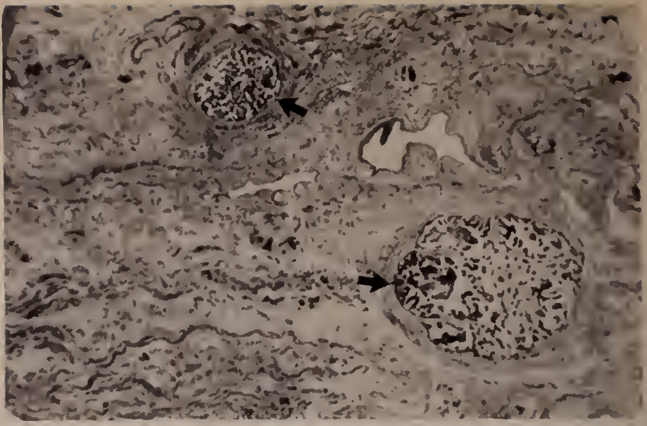

FIGURE 4. Histologic section of uterine wall, showing foci of metastatic carcinoma (arrows). (Hematoxylin and eosin stain, original magnification ×100.)

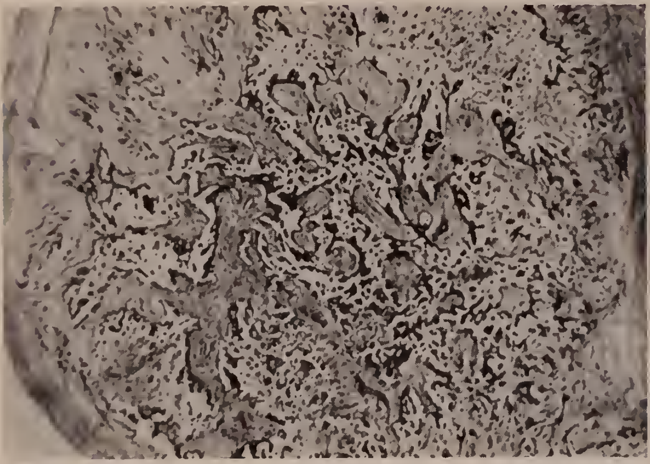

FIGURE 3. Low-power view of ovarian carcinoma, showing highly anaplastic tumor cells forming papillary projections. (Hematoxylin and eosin stain, original magnification ×100.)

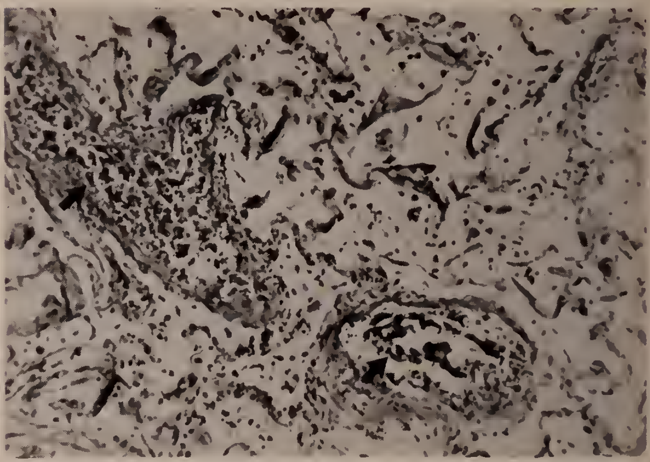

FIGURE 5. Histologic section of right lung, with tumor thromboemboli within pulmonary vessels (arrows). (Hematoxylin and eosin stain, original magnification ×100.)

tumor was bilateral.

In the abdominal cavity the tumor spread was diffuse. In the wall of the uterus (Fig 4), there were multiple foci of poorly differentiated carcinoma. Sections of the large intestine also showed multiple foci of metastatic carcinoma. Similar lesions were seen on microscopic examination of the surface of the urinary bladder, in the adrenal glands, and in the diaphragm. The liver weighed 1,350 g and was congested, but it did not show any evidence of metastatic neoplasm. The kidneys and ureters were unremarkable.

The lymph nodes were enlarged, firm, and matted in every area of the body. Sections from the para-aortic, pericolonic, peripancreatic, mediastinal, and cervical nodes showed that the architecture was to a great extent replaced by anaplastic tumor cells.

There were bilateral pleural effusions in the thorax. The right lung weighed 410 g and the left 350 g. The cut surfaces showed mild congestion but no gross evidence of pulmonary edema. Within the pulmonary vessels were tumor thromboemboli, no doubt leading to the patient's respiratory distress (Fig 5).

The heart weighed 310 g. Except for a mild increase in the thickness of the left ventricular wall (2.2 cm), the heart was unremarkable.

In summary, this patient had bilateral, poorly differentiated carcinoma of the ovaries, with extensive metastatic spread throughout the body. Her dyspnea may be attributed to massive bilateral pleural effusions and to the presence of numerous small tumor emboli in the pulmonary vessels. In addition, the neoplastic invasion of the diaphragm may have contributed to the patient's respiratory distress. Left ventricular hypertrophy, calculi in the gallbladder, congestion of the liver, and a small fibroma of the right kidney were additional autopsy findings.

An autopsy study of ovarian carcinoma at Johns Hopkins Hospital included 87 cases seen between 1927 and 1970.[4] The epithelial variety constituted 82% of these carcinomas. There were nine cases of germ cell tumors and six cases that were classified as "other tumors." These investigators could not subclassify the epithelial tumors in the known categories of mucinous, serous and endometroid, since most of these tumors were poorly differentiated. The mean age at autopsy of the patients with epithelial ovarian neoplasms was 58.6 years, with a range of 35 to 89 years. In more than 90% of these cases the patients were in Stage III and Stage IV at the time of autopsy. Stage III indicates the presence of tumor outside the pelvis; and Stage IV, distant metastases.

The autopsy findings in this group of patients showed that ascites was very common (70% of cases). Ascites in a woman should raise the suspicion of ovarian carcinoma. The peritoneum and the intestine were involved in almost 90% of the cases; the data showed that this tumor has a predeliction for mesothelial surfaces. The liver was involved in 71% of the cases, although this was not found in our case. The spleen was involved in 47% of the cases, the pancreas in 24%, and the adrenal in 21%. The lungs were involved in 44% of the cases; the tumor involvement was usually a consequence of spread to the pleura with secondary direct extension into the lung parenchyma. Lymphatic spread occurred in 75% of the cases. The lymph nodes most often involved were the abdominal, mesenteric, retroperitoneal, and pelvic; the cervical, axillary, and inguinal nodes were involved less frequently.

The cause of death in about one quarter of the cases was classified as "primary tumor death"; included in this category were patients with progressive cachexia, sepsis, electrolyte imbalance, or cardiovascular collapse. Bowel obstruction was a common cause of death; this was expected because of the prediliction of this tumor for implantation on mesothelial surfaces. In about one fifth of the cases, the patients died from a complication of therapy. Pulmonary embolism was the cause of death in 11% of the cases. This figure is rather high. It is likely that enlarged tumor-involved retroperitoneal nodes could cause venous stasis and predispose the patient to thromboembolic phenomena. Ureteral obstruction was the cause of death in only 4.2% of the cases. Other diseases led to the patient's death in 12% of the cases.

This study shows that ovarian cancer can be a catastrophic disease. The large mesothelial surfaces are involved by extensive metastatic spread; the peritoneal cavity is invaded early. This contributes to the far-advanced stage of the tumor when the diagnosis is first made. Unfortunately, at the time of initial presentation, from 60 to 70% of the patients are in Stage III or Stage IV.[5] There are some discrepancies between the degree of reported lymphatic spread at autopsy and the degree of lymphatic involvement appreciated at laparotomy for ovarian carcinoma. In a series of 190 cases of ovarian carcinoma diagnosed at laparotomy and reported by Bernstein,[6] only 5% of the patients had pelvic lymph node involvement. This is in contrast to autopsy findings in which more than 80% of the patients had pelvic lymph node involvement.[7] A reasonable explanation is that the autopsy is performed at a more advanced stage of the disease. Lymphatic spread is important and more common than the hematogenous route. The latter is infrequent, but it does occur, as demonstrated by isolated parenchymal lesions and by bone marrow infiltration.

Alvin Gelb, MD (Chief, Division of Gastroenterology, Beth Israel Medical Center): Hindsight is always better than foresight, but in retrospect, this was a woman who presented with leg edema and ascites. Unexplained leg edema in a female patient is an indication for a pelvic examination. Even after the diagnosis of carcinoma was made by lymph node biopsy, it would still be necessary to search for a primary lesion. Chemotherapy for ovarian tumors such as this one can be very effective, with good prognosis over at least one to two years. As Dr Cipolla said, one should think of a pelvic or ovarian neoplasm, and a pelvic examination and a pelvic CT scan should be carried out in such cases.

Dr Barek: The ascites, even on the initial CT scan report, was confined to a small patch underneath the left hemidiaphragm, and poor definition of the area around the gallbladder left undecided the question of a pericholecytic collection of fluid versus a gallstone. Incidentally, cholelithiasis was found at autopsy.

Dr Cameron: The private physician indicated that a pelvic examination had been performed in his office following her first admission. As I indicated in the protocol, the patient refused further outpatient treatment.

FINAL DIAGNOSES

Poorly differentiated carcinoma of the ovaries, with metastases to the cervical, axillary, inguinal, periaortic, peripancreatic, and pericolic lymph nodes, lungs, diaphragm, adrenal glands, bladder, uterus, and colon.

Ascites.
Massive bilateral pleural effusions.
Passive congestion of the liver.
Left ventricular hypertrophy.
Chronic cholecystitis and cholelithiasis.
Medullary fibroma of the kidney.

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The other side of the insulin story: Paulescu's contribution

Sam L. Teichman, md, Peter A. Aldea, md

The two names that history has linked with the discovery of insulin in 1922 are Frederick G. Banting and Charles H. Best of Toronto. However, the Nobel Prize in Medicine and Physiology for 1923 was not awarded to Banting and Best, but rather to Banting and John J. R. MacLeod "for their discovery of insulin." In fact, neither Banting nor Best nor MacLeod discovered insulin. No one can say with certainty when insulin was discovered, or by whom: Von Mering and Minkowski are given credit for first showing, in 1889, that surgical removal of the pancreas from dogs produced a condition similar to diabetes mellitus in man.[1,2] As early as 1893, Laguesse[3] correctly suggested that the islets of Langerhans, glandular structures described in 1869, secreted a substance that controlled carbohydrate metabolism. Zuelzer,[4] in 1908, and Scott,[5] in 1912, made crude pancreatic extracts trying to isolate the "anti-diabetic hormone." It is interesting to note that the name "insuline" was given to this hormone by de Mayer[6] in 1909, years before it was discovered.

These and other investigators were not discovering insulin, but were instead isolating and purifying it. The collaborative work of Banting's group was based upon the work of these prior researchers—each contributing small steps in the long march towards the goal of an insulin preparation suitably pure for use in humans.

The scientist responsible for originating the methods used by Banting's group, which proved to be the final, major steps in the isolation of insulin, was a Romanian physiologist working in Bucharest, Nicolas C. Paulescu. To this day he remains the center of a controversy surrounding the award of the 1923 Nobel Prize.[1,2]

Paulescu trained in Paris, working with Etienne Lancereux, President of the French Academy of Medicine and Chief Physician at the Hôpital de Notre-Dame-du-Perpetuel-Secours. Lancereux, in 1877, was one of the first to describe pathologic changes in the pancreas that occurred with diabetes.[7] It was again Lancereux, in 1901, who first claimed a causal relationship between pancreatic pathology and diabetes.[8] Paulescu began his research on diabetes under the direction of Lancereux.

At the completion of his training, Paulescu declined an offer to remain in France and returned to Romania in 1901, where he assumed the Chair of Physiology at the Faculty of Medicine in Bucharest, a position he was to hold until his death in 1931. His early work on endocrine physiology and pathology focused on the pituitary gland, and earned him an international reputation in this field; this led to a warm friendship with Harvey Cushing.[9] Paulescu resumed work on the pancreas and diabetes in connection with research on the formation of glycogen in the liver. He found that an aqueous extract of the pancreas, injected intravenously into a diabetic dog produced an immediate, although transient, hypoglycemic effect. War and the German occupation of Bucharest forced him to postpone publication of his findings until 1921.[10]

After some preliminary abstracts appeared early in 1921,[10] Paulescu published a comprehensive paper entitled, "Research on the role of the pancreas in digestion," in August of that year.[11] Paulescu reviewed the fact that total destruction of the pancreas produces exocrine disorders—"troubles digestifs," and three physiologic disorders: hyperglycemia associated with glycosuria, an increase in blood and urinary urea, and ketosis associated with ketonuria. In a series of 12 experiments, Paulescu examined the effects of a pancreatic extract on glucose, urea and ketone levels in diabetic dogs and compared them to the effects in normal dogs. As further controls he used the effects of injections of serum and splenic extracts into the blood of diabetic dogs and of a spinal injection of a pyrogenic substance.

The dogs were made diabetic by pancreatectomy, without surgical pretreatment of the pancreas. Paulescu's pancreatic extract, which he named "pancréine," was prepared from the surgically removed pancreas. The gland was first ground under aseptic conditions, then distilled water was added and the mixture was left on ice for 24 hours. It was then filtered and 0.7% saline solution was added to the filtrate to prepare it for injection into the jugular veins of the experimental animals.

Paulescu demonstrated that injection of this extract into diabetic dogs caused a reduction in blood and urine levels of glucose, urea and ketones. His results agreed with the current understanding of insulin physiology. In the presence of insulin, the major substrate of metabolism is carbohydrate. When insulin is withdrawn, as in diabetes, glucose utilization is impaired, and metabolism converts to fat and protein degradation. Glucose accumulates in the blood and, as its levels rise, begins to appear in the urine. The degra-

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From the Department of Cardiology (Dr Teichman), Montefiore Medical Center, Bronx, New York and the Department of Plastic and Reconstructive Surgery (Dr Aldea), Stanford University Medical Center, Stanford, California.

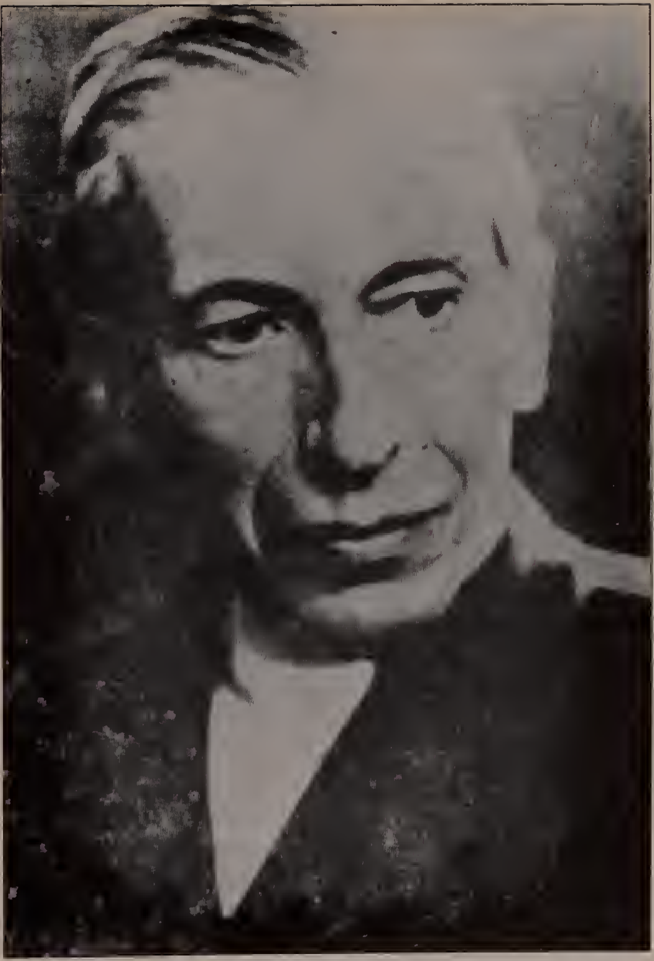
Address correspondence to Dr Teichman, Cardiology Fellow, Department of Cardiology, Montefiore Medical Center, Albert Einstein College of Medicine, 111 E. 210th St, Bronx, NY 10467.

dation products of fats and proteins are ketones and urea, respectively, which appear in increasing amounts in the blood and then in the urine as well. Paulescu demonstrated, although he was not aware of it, that when insulin is replaced, there is a conversion back to carbohydrate utilization, with a resultant fall in blood and urine glucose levels (due to increased uptake and metabolism by cells), and a fall in ketone and urea levels (due to a decrease in fat and protein catabolism). Paulescu also showed that the effects of the pancreatic extract were not limited to diabetic animals. The intravenous administration of the extract to non-diabetic dogs caused a decrease in blood glucose and in blood and urine urea levels as well.

Paulescu also conducted three controlled experiments to eliminate conflicting contentions concerning his results.[11] First, he addressed the possibility that *any* intravenous injection might have a similar hypoglycemic effect by showing that the simple injection of serum had no such effect. He then addressed the possibility that any visceral organ extract would have the same metabolic effects as the pancreatic extract. By injecting a splenic extract, prepared in a manner identical to that of his pancreatic extract, Paulescu demonstrated that no anti-diabetic effect was elicited. Lastly, he confronted a problem that had caused Scott[5] and other investigators to abandon attempts to treat diabetes with pancreatic extracts: the pyrogenic nature of the extracts. In all of Paulescu's experiments, the injection of the extract caused a low-grade febrile reaction in the animals; the increase over the baseline temperature, however, never exceeded 1.5°C. The possibility, therefore, existed that the extract brought about its hypoglycemic effect via this non-specific febrile reaction, rather than by a property inherent to the extract itself. To test this assumption, Paulescu injected a protein preparation into the spinal canal of pancreatectomized dogs that caused fevers as high as 2.0°C above the baseline. This fever, however, was not accompanied by any reduction in the blood and urine levels of glucose or urea. In fact, the injection caused a small increase in the blood levels of glucose and urea. This is consistent with the more recent clinical observation that fever usually causes a worsening of hyperglycemia in diabetic patients.

A few months after the publication of this paper, Paulescu received a letter from Scott, then at Columbia University in New York, dated November 5, 1921. He related the results of his own work with extracts, published in 1912, almost a decade earlier. Scott stated that even though his measurements were limited to glucose in the urine, he nevertheless had arrived at similar conclusions concerning diabetes and the pancreas: "... there can be little doubt ... of the existence of a pancreatic secretion, that, via the bloodstream ... finally alleviates some of the symptoms of diabetes."[12]

In February of 1922, Banting and Best published a paper entitled, "The internal secretion of the pancreas."[13] This paper reviewed some of the literature concerning diabetes and the use of pancreatic extracts to treat diabetes, and referred to one of Paulescu's abstracts published in 1921 where the data from the paper discussed above were reviewed. In their paper, there is a crucial misrepresentation of Paulescu's work, stating that "... injections [of Paulescu's extract] into peripheral veins produce no effect and [that] ... second injections do not produce such marked effects as the first." The statement does not accurately reflect Paulescu's data and contradicts itself. Some years later, Best was to attribute this to "... an error in our translation of Professor Paulescu's article."[14] Banting and Best went on to conclude from the literature that, "... the islands of Langerhans are essential in the control of carbohydrate metabolism."[13] The paper reviewed in detail the results of their experiments in pancreatectomized dogs treated with a pancreatic extract. Their extract was prepared from animals in which the main pancreatic duct was ligated, allowing the exocrine pancreas to degenerate while leaving the islets intact. An aqueous suspension was then made of the remaining tissue and, after being partially frozen in ice, an aqueous extract was prepared.


Nicolas Constantin Paulescu (1869–1931).

After presenting the results of different experiments involving intravenous injections of the extract, Banting and Best concluded,

> In the course of our experiments we have administered over 75 doses of extract from degenerated pancreatic tissue to 10 different diabetic animals. Since the extract has always produced a reduction of the ... sugar [in] the blood and of the sugar excreted in the urine, we feel justified in stating that this extract contains the internal secretion of the pancreas. ... Injections of ... saline do not effect the blood sugar [and] similar quantities of extracts of other tissues [liver and spleen extracts prepared in a similar

> manner to the pancreatic extract] do not cause a reduction of blood sugar.[13]

It is difficult when reading this historically important paper to overlook the obvious similarities, if not duplications, of the work published by Paulescu almost a year earlier. The only major difference was that Banting and Best pretreated their dogs by ligating the pancreatic duct prior to pancreatectomy. They subsequently abandoned this cumbersome procedure and began using pancreatectomy without surgical pretreatment.[15] It is clear that Banting and Best had completed experiments that led them to conclusions similar, if not identical, to those reached by both Paulescu and Scott based on their own independent research done years earlier. Banting, a surgeon by training, had become interested in this work in 1921, after reading of the research of other investigators in the field.[16] He then began work in MacLeod's laboratory and was assisted by Best, a medical student at the time.

Thus, it came as a surprise to all of the scientists mentioned above, and to the entire medical community, when the Nobel Prize in Medicine and Physiology for 1923 was awarded to Banting and MacLeod "for their discovery of insulin."

In presenting the award, Professor Sjöquist of the Karolinska Institute of Stockholm acknowledged previous efforts in the field:

> Many of these [earlier] investigations failed, while others succeeded in actually producing extracts or juices which, when injected into the blood of diabetic dogs or even human beings showed themselves able to bring down the increased content of sugar in the blood, to diminish or even stop altogether the excretion of sugar into the urine, and to bring about an increase in weight. Among these I should like especially to mention Zuelzer, . . . and also Forschbach, Scott, Murlin, Kleiner, Paulesco and many others. . . . It could be prophesied with a very great degree of probability that such a substance as insulin some day would be produced from the pancreatic gland, and much of the work had been done beforehand by previous investigators, several of whom very nearly reached the goal. Consequently, it has also been said that its discoverer was in a preeminent degree favored by lucky circumstances. Even if this be so, yet there would be cause to remember Pasteur's words: 'La chance ne favorise que l'intelligence preparée.' [sic] The Professorial Staff of the Karolinska Institute has considered the work of Banting and MacLeod to be of such importance theoretically and practically, that it has resolved them the great distinction of the Nobel Prize.[17]

The controversy surrounding this Nobel Prize began almost immediately: Banting, angered that MacLeod rather than Best was the co-recipient of the award, announced without hesitation that he would share both the award and the honorarium with Best.[18] MacLeod subsequently announced that he would share his prize with J. B. Collip, the fourth member of the group in Toronto.[19]

But what of Paulescu? If it can be said that Banting and Best discovered insulin, then didn't Paulescu do it as well? And if so, then he clearly did it by 1921, as his work was published nearly a year before Banting's and Best's work appeared in the literature. In fact, Paulescu's paper is one of the references in their work, even though it is mistakenly represented. And what of all the other scientists whose work preceded Banting's and Best's? Didn't Paulescu and they deserve more credit than the "honorable mention" contained in Professor Sjöquist's speech?

Many publications that appeared in the international medical literature after the Nobel Prize was awarded were of the opinion that Paulescu's work was equivalent to Banting's and Best's and that he deserved special credit for it. In 1923, Murlin wrote, ". . . mention should be made . . . of the favorable results reported by Paulesco (1921). . . . He found that the intravenous injection of a sterile extract into depancreatized dogs brought about a diminution or even a temporary suspension of the hyperglycemia . . . and the excessive production . . . of urea and acetone bodies."[20] Funk, in 1925, in Paris, wrote, "In 1920 and 1921 [sic], Dr. Paulesco [sic] of Romania, and Drs. Banting and Best of the University of Toronto proved in a decisive manner that the pancreas contains an anti-diabetic substance that has been given the name of insulin."[21] Lastly, in Berlin, in 1934, Trendelenburg wrote, "Shortly before the description of the discovery of insulin (1921) [sic], Paulesco [sic] achieved full success with extracts which lowered the blood sugar of pancreatectomized dogs within one hour of parenteral administration."[22]

In the years following the awarding of the Nobel Prize, Paulescu himself sought to establish his priority in the discovery of insulin. In 1924, he published a paper entitled "Treatment of diabetes (documents establishing priority)."[23] He reviewed the chronology of his own experiments, their results, and the publications in which they appeared. He discussed his isolation of the "active principle" of the pancreas, which he named "pancréine," and how he established a unit of measurement for it. He stated that on April 10, 1922 he had received a patent from the Ministry of Industry and Commerce in Romania entitled "Pancréine and its method of preparation." It was at this point, he said, that the Canadian doctors had declared that they had discovered the treatment for diabetes. Paulescu went on to review Banting's and Best's work which, he felt, was inferior to his own, and in comparison, incomplete and inadequately documented. He ended by saying that, "it seems to me that I have the right, and even the duty, to re-establish the truth and to protest against a process, never permitted in science, in re-establishing the facts with total accuracy."[23]

Paulescu's embitterment and disappointment are clear from the above paper. His disillusionment of the international medical community was evident in the following quotation from a volume of his textbook of medicine published in 1930:

> Formerly, I used to believe and taught that a scientist may work in safety, because I was convinced that the date of his publications sheltered him from any iniquity. Unfortunately, today, I am forced to acknowledge that I was completely wrong.[24]

During his lifetime, Paulescu was never to receive any acknowledgment of his contribution to the discovery of insulin, nor of his efforts at recognition. In spite of this, he did not neglect his other research. In 1923, he published the results of his further attempts at purification of insulin.[25] He studied the effects of acidic and basic solutions, heat and alcohol on the impurities in his extract and found that none of these methods made it more suitable for use in humans. Also in 1923, he published the results of experimental administration of his extract via different routes.[26] He found that enteral administration, both oral and rectal, was ineffective in producing a hypoglycemic effect in diabetic animals. However, subcutaneous administration of the extract caused a suppression of hyperglycemia and glycosuria similar to that obtained with intravenous administration. This presaged present clinical experience with insulin which is still given only intravenously or subcutaneously.

In 1924, Paulescu published a paper entitled, "Pathogenesis of pancreatic diabetes." [27] In it, he presented a fascinating, but not fully accurate, explanation of the pathogenic mechanisms he thought were involved in the abnormalities in blood levels of glucose, urea and ketones seen in diabetes. Levels of all three of these metabolic products rise upon withdrawal of insulin, but not for the same reasons. Glucose levels rise due to a decrease in its utilization, while urea and ketone levels rise due to an increase in protein and fat degradation. In this paper, Paulescu postulated that once in the digestive tract, foodstuffs are acted upon by pancreatic enzymes and are broken down into amino acids, monosaccharides, glycerine and fatty acids. They are absorbed in these forms, but are reconstituted into elaborate sugars, fats and proteins in the walls of the intestine and are found in the blood in these latter forms. However, Paulescu proposed that once in the blood, they all combined in specific proportions, along with certain minerals, to form a complex that was necessary for the proper nutrition of cells. Paulescu named this complex "plasmine." It was his claim that plasmine was formed under the influence of the pancreas and that pancréine (insulin) was the "cement," the glue that held the complex together and allowed its utilization by cells. In diabetes, without pancréine, plasmine was not formed, and its component parts—the glucose, fats and protein—remained dissociated in the blood. This accounted for the observed increase in glucose in the blood and its elimination in the urine. Fats and proteins also accumulated, but as they did, they were broken down into urea and ketones and then eliminated. In addition, Paulescu continued, in the absence of plasmine, cells did not receive adequate nutrition, thus explaining the malnourishment seen with diabetes. When pancréine was replaced, he said, this "synthesizer" helped reform plasmine and lowered blood glucose, urea and ketones. He pointed to the renewed formation of glycogen in the liver after pancréine administration, documented in his own laboratory, as proof of renewed cellular nutrition.

It is interesting to note that despite the possession of correct data on insulin's effects on glucose, urea, ketones, and even glycogen, Paulescu's inferences concerning the actual pathophysiology of the abnormalities observed in diabetes reflect a fundamental misunderstanding of the processes involved. This understanding was to come years later with much more sophisticated methods of analysis, but was to be based, nevertheless, on the experimental data recorded first by Paulescu.

Paulescu's other work showed him to be a creative and meticulous scientist and physiologist. In addition, he coauthored a five-volume textbook of medicine with Lancereux, and authored a three-volume textbook of medical physiology that enjoyed widespread use in Paris and Romania. His dedication and compassion was illustrated in the following quotation which he often repeated to the many students that he taught:

> When you enter in any hospital, divest yourselves of anguish, of guilt, and of pride . . . cast off any laziness [from yourselves] and give as much as you can to the patients, . . . you should be grateful to them, for if you care for them, they will allow you to teach yourselves. . . . And, following the precepts of Charity, take care of the patient, whoever he may be, not as a man, not as a brother that suffers, but as is appropriate [in the eyes of] God.[28]

In 1931, Paulescu died of bladder cancer after a long and painful illness. His obituary appeared in French and Romanian journals but his death went largely unnoticed in the international medical community.

Fifty years after the discovery of insulin and 40 years after Paulescu's death, the International Diabetes Federation set up a special committee to study the work that led to this major scientific accomplishment. This was done, in part, at the request of members of the Faculty of Medicine of Bucharest led by Dr I. Pavel.

Their report was published in May 1971.[29] They began, as many authors had done before them, with a concise summary of the early work in diabetes, beginning with Von Mering and Minkowski in 1889 and ending with Scott in 1912. They then reviewed the work of Banting and Best and Paulescu in detail. The last section of their report was entitled, "The discovery of insulin," wherein they stated the following:

> If the isolation of a substance involves the preparation of it in pure form . . . Banting and Best did not isolate insulin. What they did was to produce for the first time pancreatic extracts containing that substance which were suitable for subcutaneous injection into animals and man, such treatment being highly effective in controlling the symptoms of diabetes mellitus in diabetic dogs and human patients.[29]

The report then quoted the misrepresentation of Paulescu's work in Banting's and Best's original paper, along with Best's explanation that it was due to an error in translation. It went on to say that,

> There can be little doubt that Paulesco, as well as Banting and Best, obtained a pancreatic extract which contained insulin, and that the pancréine and the insulin present in the crude extracts in which the hormone was first obtained, are the same substance. . . . Had Banting and Best's researches not constituted a platform on which was erected the extensive machinery needed for the worldwide production of insulin in a form suitable for the treatment of diabetic patients, Paulesco and his colleagues may very well themselves have succeeded in ultimately achieving what was accomplished so speedily in North America. . . . [Paulesco's] exacting and time consuming measurements (on hyperglycemia, glycosuria, acetonemia, acetonuria and blood urea), matters which Banting and Best did not then study . . . may have delayed the completion of [Paulesco's] investigations, essential for the preparation of the bland pancreatic extract that was needed for the fruitful application to the relief of human suffering of the results of a fundamentally important laboratory investigation.
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> Undoubtedly, Professor N. C. Paulesco should be given special credit for the successes with which his experimental observations were crowned. But more than experimental physiology was needed if insulin was to become available in the form, and on the scale, in which it was quickly needed for therapeutic use.
>
> The Nobel Prize that was given to Banting and MacLeod was awarded for work which the Professorial Staff of the Karolinska Institute considered to be of great importance, theoretically and practically. The practical importance of the investigations initiated by Banting and Best is witnessed by the fact that since 1922, countless numbers of diabetic people have been able to lead normal lives.

If the Nobel Prize was awarded for the "platform on which was erected the extensive machinery needed for the worldwide production of insulin," then the appropriate people received it, but it was awarded prematurely, since this "platform" was constructed with the assistance of Eli Lilly Co, subsequent to the award. It could even be said that the "platform" was built because the Nobel Prize focused the world's attention on the work being done in Toronto and its obvious potential for clinical (and financial) benefit.[30]

The discovery, isolation and purification of insulin is one of the milestones of modern medical science. As is the case with most major advances, many people contributed to the final result. The controversy concerning whose contribution was the *most* significant and thus meriting the *greatest* praise and the Nobel Prize will never be settled. Geographic and perhaps language barriers caused scientists working in North America and publishing in English to receive credit for work done first in Romania and published in French. The millions of people with diabetes who have benefitted from the use of insulin should give thanks to Banting and Best (and MacLeod, Collip and Eli Lilly & Co); but *they* should have given thanks to Paulescu.

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A foreign physician in Russia in the 1930s

JULIUS D. KROMBACH, MD

Berlin, 1933. I had a promising general practice in Germany's capital, when Hitler usurped power and was on his way to becoming the dictator of Germany. Many of my male patients began to appear in my waiting room wearing the brown stormtrooper uniform. They spontaneously assured me of their immediate assistance in case anyone should cross me. But I did not intend to stay where I was not wanted.

I resolved to leave the Fatherland a soon as possible—with the full intention to return when the spook was over, which in my innocence I thought would happen within a year. But where to go in the meantime? Most countries had closed their doors to refugees from Germany, and none permitted physicians from Germany to practice medicine—except for the United States some time later.

I emigrated with my wife and young daughter to Yugoslavia and tried to earn a living as a salesman of medical supplies. My abilities as a salesman were about as good as a hunter with a slingshot. I longed to return to my chosen profession. Russia badly needed physicians. We sought the help of the American Joint Distribution Committee which through its Agrojoint in Russia helped transplant numerous jobless urban Jews to the country and trained them to be farmers. We had to wait a long time, but we finally got our visa. And so I journeyed with wife and child to Russia.

My destination was Novozlatopol (New Goldfield) a large Jewish *kolkhoz* (collective farm) in the Ukraine where the vast steppe stretched endlessly in all directions, not unlike the prairies of our Midwest. Only one small woodstrip near the hospital, planted by the Agrojoint, interrupted the horizon.

For some time I had been in contact with Dr Walter Finke (who later lived and practiced in Rochester, NY), a colleague from Germany residing in Novozlatopol for some time. He introduced me to the hospital, a small not very inviting building. On this occasion he asked me to look at an emaciated patient with an enlarged liver. When I started to sit down on the bed, Dr Finke whispered in my ear: "Don't sit down." "Why?" I asked. "Lice!" he whispered.

Thus was I introduced to a widespread medical problem I was not familiar with. My wife and I made it a nightly routine to examine and shake out our shirt, blouse and undergarments. But in spite of the universal presence of lice, we encountered surprisingly few cases of typhus. The opposite seemed to be true for malaria. Many people suffered from malaria, whereas this disease should have been a rarity. Mosquito larvae can exist only in water and there is practically no water in those parts of the Ukraine. The only explanation I can think of is the tiny artificial ponds which villages maintain for the cattle and for ice to be cut and stored in spring.

Even in a small community like Novozlatopol, medicine, like every aspect of Soviet life, was supervised by a party commissar. Grunina presided over the frequent *sobranje* (meeting) of all medical personnel, which dutifully applauded all guidelines from above. After one of these meetings Grunina told me that she was pregnant and demanded an abortion. I advised against it; she was in her early thirties and had only one young child. Grunina became huffy. "Julian Davidovich, in the Soviet Union we are free! A woman can choose what to do with her body! I demand an abortion!" Grunina had her abortion.

Only a few months later, during a *sobranje*, she informed us that abortions from now on were forbidden. Comrade Stalin had declared: the Soviet Union now produces enough food for everybody and that, therefore, abortions are not needed. "We all agree with Comrade Stalin don't we?" she ended her speech without blushing. Everybody agreed with Comrade Stalin about everything.

My wife worked with other nurses in the clinic. One day she cleaned and bandaged a wound a man had suffered at work. One gauze bandage was used up and while she applied a second one, the head nurse admonished her: "Charlotte Davidovna, one bandage should have sufficed. We cannot waste any bandages." Charlotte countered: "But Comrade Stalin said 'one should apply as many bandages as needed!' "

Momentarily I expected a strong rebuff, but the head nurse said meekly: "When Tovarich Stalin said this, it is all right." On the way home I stormed at my wife: "How could you say such a thing? You never read any line of Stalin!" "Of course not," she sweetly agreed, "but I know you have only to cite Stalin to be in the right."

The hospital was a catch-all. Any seriously ill patient, with or without fever, landed there—maternity cases included. For the latter there was only one room, but this did not create a real problem since most women gave birth at home. The shocking thing was that the few nurses of the hospital attended to all patients, women in labor included. Yet I cannot remember any alarming postpartum infection. This observation let me ponder about our concept of hygiene. People in this region grew up without much thought of cleanliness, but we encountered surprisingly few contact

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Address correspondence to Dr Krombach, 413 Georgia Ave, Crystal Beach, FL 33523.

infections. Could growing up with dirt from the first month of life on provide children with an increased immunity?

During my second year in Novozlatopol a small hospital for infectious diseases was slowly built, modestly furnished and miserly equipped. It was opened not too soon. Rumors had reached us that a gigantic wave of scarlatina was spreading rapidly from distant regions and nearing our territory. Soon villages in our neighborhood were hit and a few days later our new hospital was overfilled. All the patients were children; all suffered from Scarlatina with high fever and apathy, and many were delirious. Most of them recovered within a week, but a few got worse. When I examined their throats, the tonsillar and the whole pharyngeal region looked shockingly black, a mass of subcutaneous bleeding. Every one of them died within two or three days. We felt depressingly helpless.

I do not know whether sulfanilamide was already invented and introduced in 1937 in Europe and America. We certainly had not heard anything of the new magic bullets.

The mainstay of food in Russia was *kapusta* (cabbage). Chickens, pigeons and some vegetables could be bought on the weekly free market in limited quantities. But beef appeared only once during my stay in Novozlatopol, and this joyous event ended in outright frustration. I was asked to come to the village store in a hurry. When I arrived the entrance was blocked by an excited crowd. Inside I found an unhappy veterinarian pointing at the hind-quarter of a cow. The carcass was covered with crawling maggots. "Do you think all the meat has to be condemned?" he asked me. "Of course," I said, "there can be no question about it. But why ask me? You are the Vet!" He squirmed. "You are right, of course, but I cannot decide this by myself. I might get in trouble."

For the first time I realized how afraid people were to shoulder responsibility. I was reminded of this frequently by our dentist, a lovely elderly lady from Leningrad.

"Julian Davidovich," she used to say, "do not assume so much responsibility," when I treated precariously ill patients locally instead of sending them to the big city of Dnjepropetrowsk, saving them a dangerous 24-hour delay besides exposure.

One day a schoolteacher brought to the clinic his crying two-year-old son with a highly inflamed phimosis. I told comrade Abramovich that a circumcision would cure his son's trouble in a short time. He blanched and implored me to try everything else but that. I did not understand. "They will say I had it done for ritual reasons," he lamented, "and I will lose my job!" I could not believe it yet I tried to oblige, but two days later I had to circumcise the boy. A few months later comrade Abramovich vanished in the net of the NKVD (abbreviation for the secret police at that time). When I went to Russia I was not aware of the fact that Stalin's long lasting, bloody purge was in full swing.

Dr Chersonsky was the third and the only physician in Novozlatopol, residing there for a number of years. He was also the nominal head of the hospital. One day he informed me that he had to go on *kommandirovka* and asked me to take responsibility of the hospital for a fortnight. Kommandirovka for a physician meant an order to take a refresher course. After his departure in the forenoon I made the rounds in the hospital a few hours later and found a woman in the maternity room totally exhausted from labor, the baby dead and one arm hanging out of the vagina.

"Did Dr Chersonsky make the rounds before departing this morning?" I asked the nurse. "He did," she answered. "Did he see this woman with the baby's arm hanging out?" "Yes." "When did you and he first see her in this condition?" "Yesterday evening."

Before leaving Chersonsky had told me of a few cases requiring special attention without mentioning this woman at all. He was apparently glad to escape the responsibility for a mess he could not handle and to let me sweat it out. I saw no other way but to decapitate and remove the baby without further delay. I had never done this operation before, but luckily I had brought my Bumm (classic German book on obstetrics) with me and also my obstetrical instruments. After having finished the operation, by kerosene light, I told the nurses to bury the body. During my next round I looked into the toilet. Novozlatopol had no sewage disposal or septic tanks. The toilet facilities of the hospital could be best described as an indoor-outhouse. I found body and head of the baby at the bottom of the toilet. Indignantly I upbraided the unhappy nurses. They pointed out the difficulties. It was winter and the earth was frozen under the snow. But I insisted, of course, and the baby was removed without further delay.

Two months later, after the snow had melted, a rumor ran through the community about the murder of a baby. A body had been found in the woods and a head next to it. I was arrested and spent the next eight months in the NKVD jail in Dnjepropetrowsk. Dr Finke was not jailed, just expelled from the Soviet Union, and so were my wife and child. The Russian jail was better than a German concentration camp, but only by degrees. The overcrowding could not have been worse anywhere and the nourishment—mostly soggy black bread—was near starvation level. Almost all the inmates were political prisoners, incarcerated like myself for no plausible reasons, destined to do slave labor in the woods or mines of Siberia.

It sounds almost funny. Jail was the only place of some kind of freedom in the Soviet Union—freedom of thought and speech. Only there were people not afraid to criticize and tell jokes about the NKVD and occasionally even about Stalin. But not once did I hear criticism of the Soviet system. The suppressing regime was accepted without question, since nobody ever had known or lived under a freer one!

Against my premonition I was not shipped to Siberia, but in the end to the Polish border. After a tearful reunion with my family and another year's delay in several European countries we sailed to New York during the first days of the second World War. There was much fear among the passengers about the chance of being torpedoed by a German submarine. But we enjoyed the sea voyage. After our harassing experiences the remote possibility of drowning could not frighten us much.

As our ship (Champlain) traversed New York harbor I greeted Miss Liberty with heartfelt reverence and said to my daughter solemnly: "Now we are in America!" My little girl who had wandered for six years from country to country did not seem impressed and asked: "Where do we go from here?" "Here we shall stay forever," I answered firmly. Marianne favored me with a doubtful glance and said, "You must be kidding, Papa."

Disseminated infection with *Mycobacterium avium-intracellulare*

T. K. GEORGE, MD, RICHARD J. SCHUSTER, MD, JAMES B. WOOD, MD

It is known that nontuberculous mycobacteria can cause infections that mimic tuberculosis. This subject has been reviewed by Wolinsky.[1] These infections are confined to lungs, bone or lymph nodes; however, several cases of disseminated nontuberculous mycobacterial infections have been recognized.[1-6]

Since Cuttino reported a case of disseminated *Mycobacterium intracellulare* in 1949,[7] at least 30 cases of disseminated disease due to group III bacilli have been reported.[1] Cases have occurred in all age groups and often in association with a hematologic disorder or immunosuppressed state.[1,2,4-6] The organism has been resistant to therapy, and mortality from this disease approaches 75 percent.[1] A regimen employing multiple drugs used in the treatment of tuberculosis is the favored therapy. Early recognition of these organisms as the causative agents is imperative to enable prompt, selective antimicrobial therapy, as successful treatment may be achieved.

CASE REPORT

A 19-year-old woman was admitted to The Genesee Hospital in Rochester, New York in October 1980 with a nonproductive cough, rhinorrhea, night sweats with fever, weight loss, fatigue, and dizziness of one month's duration.

Her medical history included admissions to two other hospitals within the preceding two years for pneumonia. The first episode, an admission to Strong Memorial Hospital in Rochester, New York at age 17, was documented by culture results as meningococcal pneumonia associated with pancytopenia. A bone marrow aspirate during that admission was noncontributory. A careful review of the hospital records showed no evidence to suggest mycobacterial infection. A purified protein derivative test result was negative. The second admission for pneumonia was at age 19 at a Long Island hospital. Although information is limited, the pneumonia was considered to be caused by a viral agent and was associated with a cavitary lesion in the upper lobe of the right lung and anemia with a normal platelet count. The total leukocyte count was normal, but a lymphocytosis was present. Little other information is available about this hospitalization. The patient was lost to follow-up between admissions.

The patient had resided in New York State most of her life except for a brief residence in Georgia several years prior to her current admission. She had smoked for five years. She was employed as a waitress; little is known about her social or sexual history. It is known that she was estranged from her family, who lived nearby, and that she was living with five men in a run-down house and may have had access to illicit drugs.

On admission the patient was febrile (oral temperature to 40.1°C) with a BP of 90/50 mm Hg. She was thin, pale, diaphoretic, and had a dull affect. The findings on her general examination and specifically her pulmonary examination were normal. There was no lymphadenopathy and no evidence of intravenous drug abuse.

Laboratory data on admission showed a hematocrit of 30%, WBC count of 1,900/mm^3 with 46% neutrophils, 9% band forms and 45% lymphocytes. The platelet count was 76,000/mm^3 and the Westergren sedimentation rate was 45 mm/hour. Urinalysis demonstrated 11 white blood cells/hpf, and the chest film showed bilateral pneumonitis.

The patient was treated with erythromycin for 13 days without response. During these initial 13 hospital days, the patient was found to be anergic with no reaction to tuberculin and control antigens (measles, mumps, and SKSD). Roentgenograms showed a persistent lingular infiltrate. Possible peritracheal and azygous adenopathy was noted on a chest film but not confirmed by a chest CT scan. No cavities were demonstrable on tomography.

On hospital day 14, bronchoscopy and transbronchial biopsy were performed; they showed nonspecific pneumonitis with intra-alveolar pigmented macrophages. No granulomas were seen. A few acid-fast bacilli were noted on washings, but their significance was uncertain at the time.

Daily delays and refusals of diagnostic and therapeutic intervention were encountered throughout the patient's illness due to an apparent personality disorder. This hampered and frustrated progress in her care.

The patient consented to a bone marrow biopsy on hospital day 20, after progressive pancytopenia developed that required packed red blood cell and platelet transfusions. The hematocrit had fallen to 26%, WBC count to 2,000/mm^3, and platelet count to 19,000/mm^3. The marrow was normocellular, except for decreased megakaryocytes and plasmacytosis. A poorly formed granuloma was noted in the biopsy specimen, as well as acid-fast bacilli on a touch preparation direct stain.

On hospital day 21 the patient was given rifampin and isoniazid therapy after a negative lumbar puncture. Due to abnormal liver enzyme levels (SGOT greater than 300), isoniazid therapy was discontinued and intramuscular streptomycin was substituted on hospital day 24.

Multiple, tender erythematous nodules developed on the lower extremities on hospital day 24. Biopsies demonstrated acid-fast bacilli. The nodules drained black acid-fast positive material.

Due to continued worsening of liver enzyme levels associated with progressive hepatomegaly, rifampin therapy was discontinued, and treatment with isoniazid was reinstituted on hospital day 30. Ethambutol therapy was started. It was unclear if the hepatic dysfunction was due to the drugs or to progression of the disease.

The patient showed gradual improvement in pulmonary and hepatic function with defervescence until hospital day 60, when fever recurred (oral temperature to 40.3°C) associated with increased pulmonary infiltrates. Open lung biopsy and skin biopsy were performed to look for new superinfection, but only nonspecific pneumonitis and microab-

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From the Genesee Hospital, Rochester, NY.

Address correspondence to Dr George, Clinical Fellow, Medical Oncology Division, Cancer Center of the University of Rochester Medical Center, 601 Elmwood Ave, PO Box 704, Rochester, NY 14642.

scesses with intra-alveolar acid-fast bacilli were demonstrated in the lung tissue. No granulomas were documented in the lungs or skin.

On hospital day 63, rifampin was re-introduced, and the patient's pulmonary status had further deteriorated.

On hospital day 66 a possible nontuberculous mycobacterium was reported in culture from sputum obtained on admission. While preparations were made for ethionamide and cycloserine therapy, the patient died as a result of cardiopulmonary arrest.

Cultures of urine, sputum, cerebrospinal fluid, skin and lung grew *Mycobacterium avium-intracellulare* that was sensitive to cycloserine and resistant to common antimicrobials. Lung and skin cultures were obtained by sterile means during surgery. Urine and cerebrospinal fluid were attained via the traditional means of aseptic culture techniques. No other bacterial infections were identified in cerebrospinal fluid, urine, sputum, lung, or repeat blood cultures. Identification and sensitivities were made at the New York State Health Department, Albany, New York.

Autopsy findings were significant for bilateral pneumonia, hepatomegaly with cholestasis, and necrotic mediastinal lymph nodes. No granulomas were found in any organs despite the presence of acid-fast bacilli in lungs, skin and lymph nodes. It was concluded that dissemination of mycobacterium had occurred via hematogenous spread. It was believed that the absence of generalized granulomas was due to an underlying immune deficiency.

DISCUSSION

Cases of disseminated nontuberculous mycobacterial infection usually involve mycobacterium groups I and III. Within group III, *M avium* and *M intracellulare* resemble one another and form the *M avium-intracellulare* complex or simply *M avium-intracellulare*.

Predisposing conditions for nontuberculous mycobacterial infections include pneumonoconiosis, previous tuberculosis, chronic bronchitis and chronic obstructive lung disease, bronchiectasis and chronic aspiration.[1] Nontuberculous mycobacterial infections may also be related to an underlying malignancy[8,9] and, as noted, to an immunosuppressed state. Of interest are recent reports that link AIDS and disseminated infection with *M avium-intracellulare*.[5,6] In this case, we were unable to demonstrate any predisposing factor other than the immunocompromised state resulting from pancytopenia, although no specific immunologic studies were performed. It should be noted that our patient's past social and sexual history were not available. Whether the pancytopenia was a result of infection, as some believe may be the case,[4] or whether it played a permissive role in infection and dissemination as others report,[2] remains unclear.

Wolinsky[1] reported an increased incidence of *M avium-intracellulare* infections in the southeastern United States. Other areas with high incidences have been reported, such as Milwaukee[10] and western Illinois.[11] At our hospital, we have identified a significant number of mycobacterial isolates that contain nontuberculous mycobacteria. Between 1977 and 1981, 45 of 75 mycobacteria isolated (60%) were nontuberculous, the majority of them being *M gordonae* (50%) or *M avium-intracellulare* (33%). With increasing numbers of cases of pulmonary disease, malignancy and immunosuppression, and the increased recognition of immunodeficiency states, there has been an increase in reported cases of dissemination. It is important to be aware of the omnipresence of *M avium-intracellulare*. It can be recovered from natural sources such as rain water. Therefore, culture techniques must be performed with care. Furthermore, much of the population has been exposed; many will have skin test sensitivity. Infection does occur, although dissemination, such as occurred in this case, is rare. It is critical that evidence of infection-producing active disease be confirmed. This case also demonstrates the complexity of acquiring "proof" of infection. As a result, the patient did not receive the combination of drugs recommended for successful treatment.

Because of the uniformly resistant nature of this organism to antituberculous agents, recommended therapy from the National Jewish Hospital employs multiple drugs concurrently (personal communication, Dr Paul Davidson), namely, a five or six drug combination selected from the following agents: isoniazid, streptomycin, ethambutol, para-aminosalicylic acid, rifampin, ethionamide, cycloserine, pyrazinamide, viomycin, kanamycin and erythromycin. Other drugs, such as clofazimine and ansamycin (LM-427), and transfer factor have been tried with varying success.[6]

We have demonstrated the difficulties in making a firm diagnosis of *M avium-intracellulare* infection in time to affect the outcome, as well as the problems in choosing the proper chemotherapeutic agents. In this report we emphasize the need to be familiar with the natural history and course of what were once considered to be uncommon infections. One also needs to know the pharmacology, toxicities, and indications for use of some of the less common antituberculous drugs.

We wish to alert others to the fact that a nontuberculous mycobacterial infection should be included in the differential diagnosis when disseminated tuberculosis is being considered, especially in a patient with hematologic abnormalities, chronic pulmonary disease, or an immunocompromised or immunodeficient state. Our case occurred before AIDS was described. It may well represent one of the early cases, although lymphadenopathy, skin rash, and Kaposi's sarcoma were not present. As more cases of AIDS are identified, we anticipate that more cases of atypical disseminated mycobacterium infection will be noted.

Acknowledgment. Dr Howard Gruft, Director of the Mycobacteriology Laboratory at the State of New York Department of Health, assisted in identifying the organism and determining sensitivities.

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Acute appendicitis in a patient with concurrent adenocarcinoma and carcinoid tumor of the appendix

Arlen G. Fleisher, MD, Philip E. Gordon, MD, Robert R. Pascal, MD

Appendicitis is the most common cause of an acute condition of the abdomen requiring surgery. Although it affects persons of all ages, it is most prevalent during the second decade of life. In this report we describe a case of acute appendicitis in a patient with both adenocarcinoma and carcinoid of the vermiform appendix. A search of the English literature failed to reveal an identical case.

Case Report

A 72-year-old woman with a history of multiple episodes of diverticulitis was admitted to the hospital complaining of pain in the right lower abdominal quadrant. She reported experiencing nausea and vomiting for two days prior to admission and having several large bowel movements daily without gross blood or mucus. She had a history of right lower quadrant calcific enteroliths noted on abdominal roentgenograms taken 20 years previously.

On physical examination her temperature was 102°F and her BP 140/75 mm Hg. There was moderate abdominal distention, absent bowel sounds, and marked tenderness in the right lower quadrant with rebound tenderness. A 3 by 5-cm mass was palpated in the right lower quadrant. Results of rectal and pelvic examinations were negative. A leukocytosis of 15,400/mm^3 was reported. A plain x-ray film of the abdomen showed marked dilation of a proximal small bowel loop consistent with partial small bowel obstruction. Two oval calcific masses in the right lower quadrant, which had the appearance of enteroliths, were evident. The diagnosis of acute appendicitis was entertained. The patient was given gentamicin sulfate and chloramphenicol. A laparotomy was performed through a 12-cm right paramedian incision. Upon entering the abdominal cavity, foul-smelling cloudy fluid was noted. The mass in the right lower quadrant was dissected free. It consisted of loops of small bowel, cecum and a perforated gangrenous appendix with two fecaliths at the tip. The pelvis and right lumbar gutter were irrigated with saline solution, and an appendectomy was performed in the standard manner. The cecum was normal and viable as was the small bowel. The peritoneal cavity was irrigated with saline solution and an antibiotic solution. Two Penrose drains were placed into the right gutter and pelvis; they were brought out through a separate stab wound, and the abdomen was closed in layers.

The patient tolerated the procedure well. She was treated with a seven-day course of gentamicin sulfate and chloramphenicol.

Two different neoplasms were present in the vermiform appendix, one at the base, 1 cm in diameter, and one near the tip, 2 cm in greatest dimension. The former grew in compact nests in the submucosa. Its cells had uniform nuclei and abundant mucin-negative eosinophilic cytoplasm that resembled Paneth's cells. These cells contained many argyrophilic granules with serotonin and somatostatin demonstrated by the Pap-immunoperoxidase reaction[1] (Fig 1). No carcinoembryonic antigen (CEA) was present. This tumor had all the features of a carcinoid. The second tumor, which was a separate entity from the first, was composed of signet-ring cells with hyperchromic nuclei, abundant alcian blue-positive mucin, and cytoplasmic CEA (Fig 2). This tumor had no argyrophilic granules, did not produce any demonstrable hormones, and infiltrated the entire thickness of the appendiceal wall; it was considered to be an adenocarcinoma. Approximately 2.5 cm of histologically normal mucosa intervened between the two tumors.

On the 12th day after surgery, a barium enema was performed; it showed a free flow of barium from the rectum to the cecum. There was a large filling defect in the cecal cap that was presumed to be a result of postoperative edema. The mucosa covering this mass appeared abnormal. The sigmoid colon showed diverticulosis with a narrowed lumen, suggesting pericolonic fibrosis. Three days later an upper gastrointestinal series using barium was performed. This revealed a small diverticulum of the lower third of the esophagus and gastroesophageal reflux without a hiatal hernia. The stomach, duodenal bulb and sweep, and the visualized portions of the small bowel were all normal.

The patient was discharged on the 15th postoperative day with a planned readmission five weeks later for a right hemicolectomy. At that time the abdomen was again entered through a right paramedian incision. On exploration, adhesions around the cecum and a palpable mass in the cecum were evident. There was no evidence of gross tumor, of peritoneal seeding, or of enlargement of the lymph nodes, and the liver was smooth and

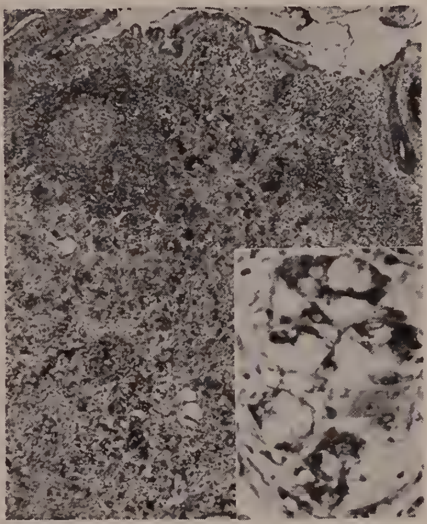

FIGURE 1. Carcinoid component is composed of solid nests of uniform cells in submucosa of appendix. Inset shows Grimelius stain of argyrophilic granules. Serotonin and somatostatin were found in the silver-positive areas. (Hematoxylin and eosin stain, original magnification ×50; inset ×225)

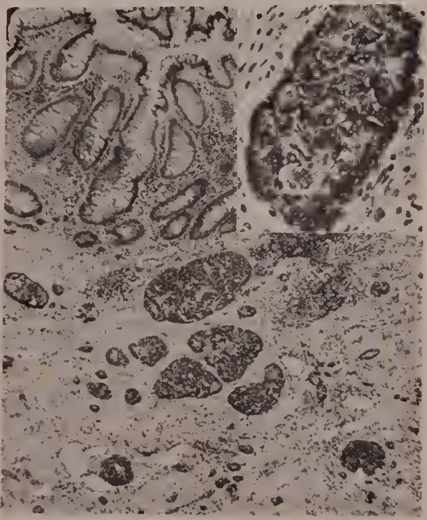

FIGURE 2. Adenocarcinoma component shows deeply infiltrating signet ring type cells whose cytoplasm is positive for CEA by immunoperoxidase reaction (inset). (Hematoxylin and eosin stain, original magnification ×50; inset ×325)

From St. Luke's Hospital Surgical Service (Drs Fleisher and Gordon), St. Luke's-Roosevelt Hospital Center, New York, NY and the Department of Pathology (Dr Pascal), Hahnemann University, Philadelphia, PA.

Address correspondence to Dr Fleisher, Surgical Resident, Surgical Service, St. Luke's-Roosevelt Hospital Center, Amsterdam Avenue at 114th Street, New York, NY 10025.

normal. The remainder of the small bowel and colon were normal to palpation. A right hemicolectomy and an ileotransverse colostomy were performed. The abdomen was irrigated with saline solution and an antibiotic solution and was then closed. The patient tolerated the procedure well and had an unremarkable recovery. No residual or additional neoplasia was discovered in either the colectomy specimen or the lymph nodes.

DISCUSSION

Intraluminal obstruction combined with bacterial invasion is believed to produce an acute inflammatory reaction that, if untreated, progresses to gangrene and perforation of the appendix.[2] Numerous entities have been described as the agent causing obstruction of the appendiceal lumen, including the common fecalith, hyperplastic lymph follicles, neoplasms, strictures, intestinal worms, and inspissated barium. Neoplasms of the appendix are uncommon; the diagnosis is rarely made before histologic examination of the specimen. Acute appendicitis is the most common clinical presentation of an adenocarcinoma of the appendix.[3] Beger,[4] in 1882, first described adenocarcinoma of the appendix. It is a rare tumor, reported in about 200 cases.[5] Histologic classification of carcinoma of the appendix can be divided into two broad categories: the well-differentiated and the microglandular types.[6] In a series of 24 cases of adenocarcinoma of the appendix, Wolff and Ahmed[6] found two cases in which the neoplasm contained foci of argentaffin cells but no cases with two distinct lesions. In addition to penetrating the wall of the appendix, adenocarcinoma spreads via the lymphatic system and the blood stream. The lymphatic and venous drainage of the appendix is the same as that of the cecum and terminal ileum. As a result, investigators[3,5-10] recommend right hemicolectomy as the treatment of choice for adenocarcinoma of the appendix. If the diagnosis is suspected at the time of appendectomy and confirmed by frozen section, an ileocolectomy should be the primary procedure. When the diagnosis is made after reviewing permanent histologic sections, a right hemicolectomy should be performed as a secondary procedure unless distant metastases are present[9] or surgery is contraindicated.[10] Hesketh[8] showed a 20 percent five-year survival for patients with adenocarcinoma of the appendix treated with appendectomy alone, compared to a 63 percent five-year survival in patients with adenocarcinoma of the appendix treated with right hemicolectomies. Other investigators[3,7] have reported that the prognosis after right hemicolectomy is significantly improved. Perforation of the appendix does not seem to alter prognosis in this situation.[5]

The carcinoid is the most common neoplasm of the appendix and constitutes 90 percent of all tumors of this organ. When located at the base of the appendix, a carcinoid may cause obstruction and contribute to the development of acute appendicitis. This tumor rarely produces metastases when less than 2 cm in size; thus appendectomy alone is usually sufficient when small lesions are present.[11]

The distinct locations and morphologic features of the two areas of tumor suggest that they were separate neoplasms, rather than an adenocarcinoid or goblet cell carcinoid.[12] That impression was confirmed by the demonstration of serotonin and somatostatin in one tumor, but no hormone production in the signet-ring neoplasm. In addition, the globlet cell variant of the carcinoid tumor, or adenocarcinoid, contains a complete spectrum of cell types from the typical carcinoid cells to goblet cells.[13] Thus, the treatment was that recommended for the more aggressive of the two neoplasms.

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Primary hyperparathyroidism in pregnancy

Serum calcium levels after parathyroidectomy

HERBERT GERSHBERG, MD, BRUCE K. YOUNG, MD

Primary hyperparathyroidism during pregnancy, though rare, is associated with a high rate of spontaneous abortion, fetal wasting and death, bone disease, and neonatal tetany.[1-3] Of nine patients who had been treated by parathyroidectomy by 1977, seven had normal infants, one had an infant with neonatal hypocalcemia, and one patient's baby died.[2] Another survey of the literature, published in 1982, found that 16 women had been operated on during pregnancy.[3] The operations were successful in 14, and 12 delivered normal infants. We describe another patient who was operated on at the end of the second trimester and who subsequently had a normal infant.

CASE REPORT

A 24-year-old nulliparous woman was admitted to University Hospital in July 1978 for treatment of hypercalcemia. She had known of her hypercalcemia and elevated serum parathyroid hormone levels (actual levels not known) for about a year. Serum calcium levels had ranged from 10.7 to 11.7 mg/dL. She had never taken any medication for the hypercalcemia.

She was approximately 25 weeks pregnant. She had no symptoms and had never had a kidney stone. Results of a physical examination were normal, with a BP of 90/60 mm Hg. The fetus showed normal development.

Laboratory data included normal serum electrolyte levels; BUN, 8 mg/dL; serum calcium, 10.8 to 11.3 mg/dL; serum phosphorus, 1.8 to 3.2 mg/dL; total serum protein, 5.5 g/dL; and albumin, 3.1 g/dL. A 24-hour excretion of urine contained 296 mg calcium and 470 mg phosphorus. Serum thyroxine level was 11.6 μg/dL; triiodothyronine resin uptake was 29%. She had a hematocrit of 37. Serum parathyroid hormone levels were 267 and 343 pg/dL (normal, 100 to 600 pg/dL).

On August 1 she underwent surgery of the neck. The left upper parathyroid gland was enlarged (0.8 × 5 cm) and was resected. The other parathyroid glands appeared normal. She had a normal postoperative course and had no hypocalcemic symptoms. The serum calcium levels in the first two days after surgery are shown in Table 1. These changes are of the same magnitude as those seen in a group of 24 nonpregnant patients with hyperparathyroidism who had preoperative levels ranging from 10.8 to 11.8 mg/dL.[4] At the time of discharge, her serum calcium level was 8.9 mg/dL. Two months later, at 33 weeks gestation, her serum calcium level was 9.6 mg/dL, and her serum phosphorus level was 3.9 mg/dL.

The patient had an uneventful prenatal course until her admission in early labor on November 27, 1978. The fetal heart rate was 140 beats/min. Pelvic examination revealed a vertex presentation, floating with the cervix 3 cm dilated. Pelvimetry showed an anterior-to-posterior diameter of 9.4 cm and a transverse diameter of 10.8 cm. After a four-hour trial of oxytocin augmentation, the patient underwent a primary cesarean section for cephalopelvic disproportion. A 3.65-kg girl was delivered with a one-minute Apgar score of 8 and a five-minute Apgar score of 9. At delivery, the umbilical cord was wrapped around the newborn's shoulder, trunk and legs. The patient's postoperative course was complicated by an endometritis that responded to antibiotic therapy. She was discharged on the eighth day after surgery.

The newborn had an uneventful hospital course. The serum calcium levels at six, 12, and 24 hours of age were 9, 9.4, and 8.4 mg/dL, respectively. At four months of age, the infant showed normal development.

DISCUSSION

During normal pregnancy, total serum calcium levels tend to decrease as serum albumin levels decrease.[5,6] In our patient, the total serum calcium levels were elevated at least a year before pregnancy and did not change during pregnancy. This emphasizes that even slight hypercalcemia is important during pregnancy and should be investigated.

The postoperative changes in serum calcium levels are worthy of comment. After subtotal parathyroidectomy for hyperparathyroidism in nonpregnant patients, the remaining parathyroid glands are partially suppressed for two to five days, as measured by decreases in urinary phosphate and hydroxyproline levels.[4] During this period, the serum calcium level falls but is usually maintained above symptomatic levels (approximately 7.5 mg/dL). In some patients, transient hypocalcemia develops. It is a popular belief, but has never been documented, that hypocalcemia occurs more often when bone calcium is depleted—the so-called "hungry bones." If this were true, one might expect that the combination of hyperparathyroidism and fetal demand for calcium would deplete bone calcium, and that after parathyroidectomy, hypocalcemia would occur. That it did not occur in our patient may be explained by the observation that pregnant women are in positive calcium balance and have normal bone calcium as measured by forearm densitometry.[7] At least two hormonal changes in pregnancy would maintain positive calcium balance: an increase in plasma level of 1,25-dihydroxycholecalciferol, which increases intestinal absorption of calcium,[8] and an increase in plasma level of calcitonin, which counteracts the bone-resorbing effect of parathyroid hormone.[9] It should be noted that in one other pregnant patient with hyperparathyroidism, for whom postoperative levels are recorded, the serum calcium level declined from 11.2 to 8.5 mg/dL, and she did not have symptoms after removal of two hyperplastic glands and one adenoma.[2]

Another explanation is that the important cause of postoperative hypocalcemia appears to be the degree of parathyroid suppression, and that bone calcium reserve is unimportant. In support of this is the observation that all six patients in whom symptomatic hypocalcemia lasting longer than a week developed had prolonged surgery with excessive manipulation of the parathyroid glands.[4] There was difficulty in identifying the adenoma; five had one or more normal glands removed in addition to the adenoma, and three were operated on twice.

It is difficult to estimate the complication rate of untreated hyperparathyroidism in pregnancy, because the literature is confusing. The most recent review of 63 cases in the world literature[3] includes many women in whom the diagnosis was made postpartum or at a

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From the Departments of Medicine (Dr Gershberg) and Obstetrics and Gynecology (Dr Young), New York University School of Medicine, New York, NY.

Address correspondence to Dr Gershberg, 614 Second Ave, New York, NY 10016.

TABLE I. Serum Calcium Levels After Parathyroidectomy in Our Patient and in Nonpregnant Patients*

Time	Patient's Serum Calcium Level, mg/dL	Changes in Serum Calcium Level, mg/dL*: Patient	Changes in Serum Calcium Level, mg/dL*: Nonpregnant Patients
Before surgery	11.1	—	—
2 hr after surgery	11.1	0	−0.5
8 hr after surgery	9.2	−1.9	−1.6
16 hr after surgery	9.1	−2.0	−1.6
40 hr after surgery	8.9	−2.2	−2.4

* Average change calculated in 24 patients, described by Hecht et al[4], whose calcium levels before surgery were 10.8 to 11.8 mg/dL.

subsequent pregnancy. The authors describe three cases, two of which were operated on during pregnancy without success. One of these patients had a normal infant and the other an infant with growth retardation. The third had a normal infant and was found to have hyperparathyroidism six weeks postpartum. Despite the absence of clear data, their estimates of 45% neonatal and 46% perinatal complication rates are consistent with those of other investigators.

The data regarding parathyroidectomy during pregnancy are more accurate. Of a total of 15 patients, including ours, whose successful operations during pregnancy are documented, 13 had normal infants.

Treatment of hyperparathyroidism during pregnancy should depend on the individual. Surgery itself carries little risk and, if indicated, should not be delayed unless delivery is imminent. If the disease is severe, as evidenced by systemic symptoms, nephrocalcinosis, and serum calcium levels greater than 12 to 12.5 mg/dL, it would be reasonable to perform surgery. Serum calcium is actively transported from mother to fetus, and high levels would be damaging to fetal growth and fetal parathyroid gland function.

Most patients are asymptomatic and have minimal hypercalcemia. Whether these patients should be treated medically during pregnancy would be a matter of individual judgment. Our patient did well after parathyroidectomy relatively late in pregnancy and delivered a normal infant. Whether she would have done as well without surgery is a matter for speculation.

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Histoplasmosis with draining lymphadenopathy

JOHANNA GOLDFARB, MD, EILEEN HILTON, MD, RICHARD SPERLING, MD, STEPHEN G. BAUM, MD

Histoplasmosis is an infection of the reticuloendothelial system caused by the organism *Histoplasma capsulatum*. Although lymphadenopathy is seen in disseminated disease, localized draining peripheral nodes have not been reported, to the best of our knowledge. We describe a patient with disseminated histoplasmosis who had necrotic draining inguinal nodes overlying a deep bone lesion.

CASE REPORT

A 52-year-old man was admitted to the Bronx Municipal Hospital Center with a draining left inguinal mass of several months' duration. He had been well until one year before admission, when a chronic cough developed. Five months before admission he had intermittent left knee pain and malaise, and he began to lose weight. Two months before admission the knee pain became constant, and he noted a swelling in the left side of his groin. One week before admission the inguinal mass began to drain pus.

He had lived in the United States for 12 years, working as a migrant farm hand in New York State and briefly as a plumber in Texas. Most recently he had been a guard at a construction site in New York City. He had no history of drug abuse, homosexuality, or blood transfusions.

On admission, he was a cachectic man in no acute distress with a temperature of 100.8 °F. A 9 × 6-cm firm, indurated erythematous mass was present on the medial part of his left thigh below the inguinal ligament. Several sinus tracts with superficial ulcerations and a purulent discharge at the skin surface were present. Extension of the left hip joint was limited by pain. The liver edge was palpable 2 cm below the right costal margin, and a spleen tip was palpable. Laboratory tests revealed a WBC of 5,300 cells/mL and a hematocrit reading of 31%. Blood chemistry results were within normal limits except for an alkaline phosphatase level of 1,265 units. Gram's stain of a needle aspirate of the in-

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From the Division of Infectious Diseases (Drs Goldfarb, Hilton and Baum) and the Department of Medicine (Dr Sperling), Bronx Municipal Hospital Center, The Albert Einstein College of Medicine, Bronx, New York

Address correspondence to Dr Goldfarb, Assistant Professor of Pediatrics, Department of Pediatrics, New York Medical College, Munger Pavilion, Valhalla, NY 10595.

guinal mass showed polymorphonuclear cells without organisms; a culture grew staphylococci that were coagulase negative. Roentgenographic examinations showed a diffuse interstitial infiltrate on chest x-ray, periarticular demineralization of the left acetabulum, and normal knee films. Computerized tomography showed destruction of the left acetabulum and a normal femoral head.

An excisional biopsy of the inguinal mass was performed on the fifth hospital day and showed a diffuse granulomatous process involving lymph nodes and skin. Areas of central necrosis and intracellular organisms characteristic of *H capsulatum* were present. Fungal cultures grew *H capsulatum*.

Further evaluation included a bone marrow aspirate, which had normal cellular elements but from which *H capsulatum* was isolated. A hip aspirate yielded 2 mL of clear sterile fluid. A morning serum cortisol was normal. Fungal blood cultures were sterile.

Treatment was begun with 200 mg of oral ketoconazole twice daily. During the next weeks, his fever abated and his pain decreased. The groin mass healed slowly with granulation, and the hepatosplenomegaly receded. He was treated with ketoconazole for one year. During this time, he remained afebrile and gained 5.4 kg (12 lb). His alkaline phosphatase level fell to 280 units. X-ray films of the hip showed healing of the acetabular lesion with filling in of the lytic lesion with new bone. A chest roentgenogram was normal, and he remained well six months after completing therapy.

DISCUSSION

Peripheral adenopathy may occur with disseminated histoplasmosis but is less common than involvement of visceral nodes.[1] Granulomas, often with central necrosis, occur as in myobacterial infections. However, necrosis of nodes with sinus tracts to the skin has not been documented with *H capsulatum* infection.

Bone lesions, as seen in this patient (although not unusual in infection with the related organism *H duboissi*), are not typical of infection with *H capsulatum*. Solitary lesions, such as in this case, can occur during the course of chronic disseminated disease.[1-5] Multiple, widespread bone lesions are described in acute, rapidly progressing disseminated disease in infancy.[6,7] A syndrome of migratory arthritis accompanying dissemination in adults has been described and is transient and appears to be an immunologic response to the infection.[8]

In our patient, the systemic nature of his symptoms as well as the pulmonary infiltrate, hepatosplenomegaly, and culture of the organism from bone marrow indicate that his disease was disseminated. The course of the disease was subacute, with focal bone and lymph node involvement predominating. Exact onset of infection is unclear, and focal exacerbation may have followed a long period of chronic disease.

Any patient in whom disseminated histoplasmosis develops may have some form of immunodeficiency.[1] The possibility that our patient had acquired immunodeficiency syndrome was considered. However, he has no risk factors, he's had no other opportunistic infection, and he has had a normal lymphocyte count throughout the course of his condition.

Our patient has done very well with ketoconazole therapy. Experience with ketoconazole in disseminated histoplasmosis is limited, however, and prolonged follow-up observation will be necessary.[9,10]

The unusual presentation of this infection by an organism that does not respond to ordinary antimicrobial chemotherapy emphasizes the need for biopsy and specialized culture techniques in the evaluation of adenopathy with sinus formation.

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NYJ NEWS FEATURES

Canada faces a change in its national health plan

An ear cocked northward in recent months might have detected yelps and yowls, evidence that a dog fight of some sort is going on in Canada. The bone of contention is a new Canada Health Act that would supplement the national health insurance plan.

Canada has had national health insurance for 15 years. The first phase, covering general hospital care, was established 25 years ago, and coverage of all doctors' services outside the hospital was added in 1969. The plan is called Medicare, but it is not to be confused with Medicare in the United States. Canadian Medicare covers everybody, old and young, rich and poor, and the majority of Canadians have forgotten what a doctor's bill or hospital bill looks like.

There is no private insurance for hospital care or doctors' services. Private insurance for anything that is covered by Medicare is not allowed. Canada has virtually no private hospitals, apart from a handful of small specialty institutions.

Medicare is well liked in Canada, and may be the most popular government program ever. The three major political parties in Canada enthusiastically support Medicare. More surprising, perhaps, the Canadian Medical Association (CMA), representing the country's medical profession, wholeheartedly endorses Medicare.

WHAT THE NEW LAW DOES

So, why is Canada getting a new law concerning a health plan that has been in existence for years? And if Canadians are so happy with Medicare, why the uproar?

The person chiefly responsible for persuading Canada that it needs a new law is the federal minister of health, Monique Begin. A warm-hearted French-Canadian idealist, Miss Begin claimed that Medicare was being eroded because charges to patients were creeping into the system. "Through a cumulation of direct charges on the sick—each one not a possibly big increase in itself—the goal of complete insurance, fully prepaid, is being abandoned," she says. She proposes that a $5 charge today might become $50 tomorrow, and eventually Canada would, once again, have two tiers of care: one for those who could pay and another for those who could not. That trend, she declares, must be stopped in its tracks. There must be no financial barriers to care. She estimates that last year Canadians paid $100 million* in extra charges to hospitals and doctors. The new law will not actually alter Medicare other than to try to eliminate those extra charges.

To understand how such charges arise even though the federal government opposes them, it is necessary to understand that under the Canadian Constitution health is the jurisdiction of the individual provinces. With 10 provinces and two territories, Canada has 12 different Medicare plans. All, however, must conform to the basic principles set out in the federal legislation in order to qualify for federal funds. The federal government provides about half of the money for Medicare.

Until now, if the provinces elected to levy token charges on patients, that was their business. British Columbia, for example, charges hospital patients $8.50 a day. But it has negotiated a deal with its doctors whereby patients cannot be charged extra for any medical services. Whereas in Ontario, the largest province, there are no hospital charges, but doctors may bill their patients and charge them more than the patients will get back from Medicare. Approximately 1,500 doctors in Ontario charge extra to some patients. The other 86 percent operate within the plan, accepting Medicare rates as full payment. They prefer the regular government cheque, have no need to send out bills to individual patients and incur no bad debts. They are paid a set fee for their service. Medical specialists are not on salary as are British National Health Service hospital consultants. Patients are free to choose their doctors. They are not on capitation lists or required, like the British, to see one particular general practitioner.

The medical professions in each province negotiate, at regular intervals, the fees to be paid by Medicare. Doctors who do not like the government fees can stop dealing with the government and bill patients on their own. This was the doctors' safety valve. The province of Quebec is an exception to that rule. There, patients of doctors who practice outside of Medicare get nothing back from the plan. They must pay the whole bill themselves. Needless to say, few patients are willing to do so.

In eight provinces doctors can increase the fees by billing their patients an extra amount, not covered by the government insurance. Most do not, although many grumble about their fees from Medicare. That is not surprising given that, for example, the fee for a double coronary artery bypass in Toronto is $866. In Buffalo, in comparison, it is $4,195. A CAT scan in Toronto pays $50.30 and a cesarian section pays $182. Nevertheless, doctors in Canada are ahead of the pack in income compared with other groups in society.

An indication of the degree of dissatisfaction comes from the number of doctors who leave Canada to practice in the United States. Canada's net loss amounts to about 300 doctors each year. During the period of wage controls, from 1977 to 1979, that number more than doubled, then dropped back again. It is relatively easy for Canadian doctors to move across the border. In fact, at almost

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* $1 Canadian = $0.77 American

“Emergency services only”

Recalling a strike by Canadian doctors

The prairie province of Saskatchewan is considered the North American pioneer of the prepayment principle of health care. In 1914, when the farming community of Sarnia was about to lose its only doctor, town officials offered him an annual retainer of $1,500. By 1930, 32 communities in the province had instituted similar tax-supported plans.

During the 1930s doctors were placed on a kind of relief, through which they could earn $50 to $75 per month by working in drought areas. Far from objecting to governmental interference, the medical profession endorsed a state health insurance program.

Perhaps because of a universally shared experience in the “dirty 30s,” the medical profession accepted the Saskatchewan Hospital Services Plan of 1947, a socialist government program to provide hospital care for all “without the ability of the individual to pay.” The plan served as a model for other provinces, and in 1958 federally shared free hospitalization went into effect on a national basis without a hitch.

But in 1959, by which time the makeup of the Saskatchewan medical profession had changed dramatically from rural GP to city specialist, and by which time the doctors' own health-insurance plans—covering 40 percent of the population—were thriving, the physicians withdrew their support of government-operated medical care insurance. When the government, still socialist, announced that a free medical care plan would go into effect on July 1, 1962, the war was on.

Amid cries of totalitarianism, communism, and fifth column sabotage, doctors lost all inhibitions. At a mass meeting of more than 600 of the province's 750 practicing physicians, the membership closed ranks behind their leaders, giving them the power to call for “emergency services only”—and in just 29 of the province's 148 hospitals—if they did not receive the right to practice outside the plan. Signs were distributed, to be displayed prominently in waiting rooms:

> TO OUR PATIENTS:
>
> THIS OFFICE WILL BE CLOSED AFTER JULY 1, 1962. WE DO NOT INTEND TO CARRY ON PRACTICE UNDER THE SASKATCHEWAN MEDICAL CARE INSURANCE ACT.

One large society specifically stated that, in addition to the office closings, there would be no home visits, no telephone advice, no prescription services, and no release of medical-legal documents.

The strike indeed occurred, and on its first day there was a widely reported death of a baby from meningitis. His parents had made a futile, 150-mile search for medical treatment, but all facilities they visited were closed. Nonetheless, the province's newspaper publishers, business community, and Chamber of Commerce supported the physicians, as did the Canadian Medical Association.

Farm and labor organizations formed the opposition. The public was split, as strike-supporting Keep Our Doctors committees vied to out-petition Citizens for Medical Care groups. The province's medical school took an ostensibly neutral stance, but all professors who publicly opposed the strike were to depart the following year. Nurses were torn by their loyalty to the physicians on the one hand and their duty and guilt on the other.

Officially, the province's response was “a strategy of silence.” But a government recruitment effort, launched before the strike began, attracted 100 new doctors (mostly British, with a few Canadian and American), who comprised half of a skeleton work force. They were vilified as scabs.

The majority of physicians were diehard supporters of the strike, but their strength waned, and a settlement was reached 23 days after the job action had begun. A face-saving measure permitted the doctors to be paid indirectly by the state through several alternate plans, but within two years physicians were to find all but direct government reimbursement too bothersome.

It is ironic that the region with perhaps the most progressive history of health-care financing became the site of the most militant opposition to universal coverage. But once again Saskatchewan physicians had become the pioneers, albeit reluctant ones, of a beneficent program of health care.

With the passage of Canada's Medical Care Act of 1968, all physicians services—home, office, clinic, or hospital—became covered, as the federal government proposed sharing 50 percent of each province's health bills. All 10 provinces passed legislation to meet the act's standards. Today virtually the entire Canadian population of 22 million is enrolled in such a provincial health plan.

Alan Blum, MD

Source: Badgley RF, Wolfe S: Doctors' Strike: Medical Care and Conflict in Saskatchewan. *Toronto: Macmillan, 1967.*

every medical conference in Canada, recruiters from Texas are in evidence offering blandishments. There are few takers.

And now there is the new Canada Health Act. It will penalize each province one dollar for every dollar a patient in the province is required to pay a doctor or a hospital. The federal government cannot ban directly extra charges in the provinces, but that is tough arm-twisting. Pressured by budget deficits, the provinces cannot afford to lose in federal funds an amount that is equal to the extra dollars that have been going to doctors from patients. The act gives the provinces three years to eliminate the extra charges. After that, the penalties begin.

THE OPPOSITION SPEAKS OUT

The medical profession has roared with fury. It is not simply the money that enrages the doctors, because extra charges to patients across Canada add up to less than 2 percent of the total doctors' bills. Their anger stems from the fact that if they are unable to bill patients extra, they will have no alternative to government-set fees. They will be civil servants, they say, with no choice but to cooperate or leave Canada.

There are predictions of an exodus greater than any seen in the past. Some top-notch specialists, including Dr. Ian Munro, internationally renowned facial surgeon at the Hospital for Sick Children, in Toronto, have declared publicly that they will leave Canada. Doctors who teach at medical schools and are used to extra-billing to make up for fees lost through time given to teaching or used to subsidize research, have said that they would not be able to afford to continue their teaching and research.

The Canadian Medical Association has argued, fruitlessly, that the new act will cause a number of problems and conflicts in the health care system. For two years it has said the key problem is that Canada spends too little on health care. Health costs account for 8.3 percent of the gross national product, considerably less than in the United States, but more than in Britain. The CMA asserts that the government should be putting in more funds, rather than taking out the little private money that now

Provincial Health Insurance Plans*

Province/ Territory	Source of Funding	Extra-billing for Insured Services by Physicians	User Charges†
British Columbia	Premiums and general taxation; premiums paid on behalf of social assistance recipients: up to 90% premium assistance for low income earners; temporary premium assistance in cases of financial hardship.	Virtually all doctors have agreed not to opt out of the plan or extra-bill. Estimated annual amount of extra-billing $0.00.	Has user charges of $8.00 per visit for day care surgical services, $10.00 for emergency services and $8.50 a day for hospital bed (estimated annual amount $35 million). Daily charge for chronic care patients.
Alberta	Premiums and general taxation; premium exemptions for elderly and very low income; premium assistance for low income.	No opting in or out required. Doctors may extra-bill if patients agree beforehand. Doctor bills plan for authorized fee and patient for extra amount, or patient for full amount. Estimated annual amount of extra-billing $13 to $14 million.	$10.00 admission charge. Daily charge for chronic care patients after 120 days.
Saskatchewan	No premiums; financed from general taxation.	Doctors may extra-bill and remain in plan by billing patient directly, who then seeks reimbursement from the plan. If patient is not charged more than plan schedule, doctor bills plan directly. Estimated annual amount of extra-billing $2.3 million	No user charges.
Manitoba	No premiums; financed from general taxation, including a 1.5% payroll tax levied on employers.	To extra-bill doctor must opt out of plan and bill patient directly. Patient applies to plan for reimbursement of plan schedule portion. Estimated annual amount of extra-billing $1.2 million.	Daily charge for patients awaiting nursing home placement.
Ontario	Premiums and general taxation; premium exemptions for welfare recipients and elderly; premium assistance for low income; temporary premium assistance in cases of financial hardship. Family premium is $56.70 per month.	To extra-bill doctor must opt out of plan and bill patient directly. Patient applies to plan for reimbursement of plan schedule portion. Estimated annual amount of extra-billing $50 million.	Daily charge for most chronic care patients.
Quebec	3% payroll tax levied on employers, and general taxation.	To extra-bill doctor must opt out of plan and bill patients directly. Patients *cannot* seek reimbursement from plan. Very few doctors opt out. Amount of extra-billing $0.00.	Daily charge for prolonged care patients.

flows in the system.

Canadians will get exactly the kind of two-tier system Miss Begin wants to prevent, according to the CMA. Canadians who can afford it will go to the United States for top medical care. It warns that if doctors lose the option of practicing outside Medicare, they will have to begin using union tactics, including strike if need be, should fee negotiations with any province fail to reach an agreement.

PROSPECTS FOR THE FUTURE

It was this very point—the right to bill patients directly and charge extra—that led to the only major strike of doctors in Canada 22 years ago. In the province of Saskatchewan, where Medicare was born, doctors closed their offices, and only emergency care was provided until the doctors won the fight.

This time around it seems highly improbable that the doctors will retain the right to bill extra. The CMA recommended, realistically, that if that right was to be taken away, binding arbitration should be mandatory in fee-negotiation disputes. Then the medical profession would not be totally at the mercy of the government, with strike its only weapon. Whether the doctors gain this concession remains to be seen, but it is not written into the new act.

For a time, the doctors hoped the act would be challenged by the provinces in the Supreme Court. Provincial health ministers were ired by what they saw as federal government intrusion in provincial matters. But these fears have been appeased by Miss Begin, who amended the act to make it clear that provincial toes would not be trod on. The doctors' hopes seem to have been dashed.

Now one can only wait and see what impact the new act will have. If Canada loses some of its best doctors, it will be tragic. If doctors have to close their offices, like unionists on strike to bargain fees, patients will be the losers. If teaching doctors stop teaching, future Canadians will suffer from lack of care.

But who can quarrel with Miss Begin when she argues that nothing must stand in the way of a sick person seeking care? "The misfortune of illness, which at some time touches each one of us, is burden enough. The costs of care should be borne by society as a whole," she insists.

Marilyn Dunlop

Miss Dunlop is a medical writer based in Toronto.

Province/ Territory	Source of Funding	Extra-billing for Insured Services by Physicians	User Charges†
New Brunswick	No premiums; financed from general taxation.	Doctors may extra-bill and remain in plan by billing patient directly, who then seeks reimbursement from the plan. If patient is not charged more than plan schedule, doctors bill plan directly. Estimated annual amount of extra-billing $0.2 million.	Daily charge for patients awaiting nursing home placements. $6.00 user charge for out-patient services.
Nova Scotia	No premiums; financed from general taxation.	Doctors may extra-bill and remain in the plan. Doctor bills plan for fee and patient for extra amount. Estimated annual amount of extra-billing $3.4 million.	No user charges.
Prince Edward Island	No premiums; financed from general taxation.	Doctors may extra-bill and remain in plan by billing patient directly, who then seeks reimbursement from the plan. If patient is not charged more than plan schedule, doctors bill plan directly. Doctors may also opt-out for all patients. Estimated annual amount of extra-billing $0.05 million.	No user charges.
Newfoundland	No premiums; financed from general taxation.	To extra-bill doctor must opt out of plan and bill patient directly. Patient applies to plan for reimbursement of fee schedule portion. Estimated annual amount of extra-billing $0.03 million.	$5.00 daily charge to a maximum of $75.00 (estimated annual amount $1 million).
Yukon	Premiums and general taxation. Premium exemptions for welfare recipients, elderly and no taxable income; premium assistance for very low income.	No doctor opted out of the plan and able to extra-bill.	No user charges.
Northwest Territories	No premiums; financed from general taxation.	No doctor opted out of the plan and able to extra-bill.	No user charges.

* Source: Health and Welfare Canada, November 10, 1983.

† Each province has unique exemptions to these charges which have not been included in the table.

THE SUICIDAL PATIENT

By Victor M. Victoroff, MD. 278 pp. Oradell, NJ, Medical Economics Books, 1983. $24.50 (hardcover).

The author's study of this subject began more than 20 years ago, when he was chief of the Division of Psychiatry at Huron Road Hospital in Cleveland. This book is the result of his observations and a systematic study of the subject, as well as experience acquired as a frequent lecturer to high schools and colleges.

Although the book is very easy to read, it is also easy to get lost in its verbosity. There is no doubt, however, that the author has a command of the subject and has tried to approach it from all dimensions.

In one chapter he exhaustively examines the epidemiology of suicide. This information is useful if one wants to understand the statistics, but less useful if one wants to remember the classical profile of individuals who are most at risk for suicide.

The author states, and rightly so, that suicide is a sign with many causes, but believes too strongly that suicide is easy to diagnose and to treat. Some of his messages and advice are worthwhile remembering: listen to the patient attentively, confront the patient with his suicidal intentions, do not be afraid to ask the right questions about suidical ideas or intentions when these are not brought up spontaneously. Also important is his advice about including the subject of suicide prevention and recognition in the curricula of medical schools.

One of the author's most important statements is, "There are never enough listeners."

The chapter that deals with physicians at risk for suicide is particularly useful, with some important tips on treatment. I find the author less skillful when he tries to examine the different arguments on the right to commit suicide. The book could have gained in value if Dr Victoroff had documented the studies from which he drew some of his conclusions about physicians at risk for suicide.

In the chapter on suicide and the law the author answers most of the questions of physicians and hospital administrators regarding the responsibilities and liabilities in suidical actions. It is explicit, brief, reliable, and it masters all of the up-to-date knowledge concerning the legal issues of dangerousness and suicidal behavior.

The book is of value as an addition to the library of those medical practitioners, especially psychiatrists, who are faced with the problem of suicide recognition and prevention in their everyday practice and as a teaching guide for general practitioners and health care workers.

HANA ROSTAIN, MD
New York University
Medical Center
New York, NY 10016

DSM-III TRAINING GUIDE FOR DIAGNOSIS OF CHILDHOOD DISORDERS

By Judith L. Rapoport, MD, Deborah R. Ismond, MA. 178 pp. New York, NY, Brunner/Mazel Publishers, 1984. $17.50 (hardcover).

"Warning: DSM-III may be hazardous to your good sense! Application of DSM-III criteria is not prescribed without prior or extensive clinical experience." This admonition, clearly boxed and heading the conclusions chapter, reflects the readable, almost conversational style of this training guide. More important, however, the "warning" reflects the authors' critical, yet approving approach to DSM-III; approving in their conviction that multiaxial formulation is essential for psychiatric diagnosis, particularly for children, and that the descriptive criteria of psychiatric symptom clusters that DSM-III provides is a basis for progress in clinical psychiatry. Yet they are critical and aware that, particularly in childhood and adolescence, syndromes may not be as distinct and separate as DSM-III suggests and that recognizing specific behaviors and their degree of impairment may not be a simple process at all. That this training guide had to be written in the first place underlines the difficulty with some of the DSM-III criteria.

With this basic philosphy, Judith Rapoport and Deborah Ismond have put together a small, typographically appealing volume in which they attempt to clarify the criteria for the various clinical syndromes of childhood and adolescence, adding to the bare criteria of DSM-III the pros and cons for inclusion of the syndrome as a distinct entity. Dr Rapoport, who is chief of the Section on Child Psychiatry at the National Institute of Medical Health and a member of the committee that formulated the section on disorders of infancy, childhood and adolescence for DSM-III, is well qualified to do this.

The book is divided into four sections and two appendices. Section I, "An overview of psychiatric diagnosis in pediatric age groups" discusses the problems in psychiatric diagnosis, the primitive state of our understanding of natural history, family patterns and developmental aspects of childhood behavior disorders, the atheoretical, purely descriptive nature of DMS-III categories, the question of their ultimate validity and the importance of multiple axis in diagnostic formulation. Section II, "Basic concepts for pediatric psychiatric diagnosis" details the use of Axis II, III, IV, and V, and outlines differences between diagnostic processes used in adult and in child psychiatry. The authors stress the importance of structured clinical interviews and of rating scales for measuring clinical severity and change. This is felt to be important in evaluating the results of psychopharmacologic agents.

Section III, "Major classifications and differential diagnosis" is the heart of the training guide. It deals primarily with diagnostic classifications that may be controversial or may be newly formulated in DSM-III. These include personality disorders in children and their parallel diagnosis in adults, developmental anomalies appearing in the first year of life (autism, pervasive developmental disorders, mental retardation, reactive attachment disorders of infancy), schizophrenia, affective disorders, attention deficit and conduct disorders, anxiety disorders, disorders manifesting a physical nature (eating disorders, stereotype movement disorders) and "other disorders" (elective mutism, identity disorders, gender identity disorders, adjustment disorders). Each of these groups is presented in a separate chapter in terms of diagnostic criteria and differential diagnosis. What makes this guide unique is an informal discussion of the problems in using each of these classifications and the clear and dramatic case vignettes that make the criteria come to life. In addition, Section III deals with Axis II syndromes (specific developmental disorders), and in a brief chapter the use of V Codes in the absence of Axis I or II diagnosis is considered.

Section IV, "Conclusions," looks forward to DSM-IV, with questions concerning the validity of Axis I disorders as distinct entities, and, as suggested by the "warning" box, the authors stress that DSM-III is not a magic formula for psychiatric diagnosis. It can only reflect the clinician's ability to identify patient symptoms.

This is more than a training guide. It expresses the thoughts of many child psychiatrists concerning DSM-III; their questions concerning the grouping of certain symptoms, their concern about the atheoretical nature of the classification and the absence of psychodynamic formulation. As a training guide it is sometimes too dogmatic (as in its insistence upon rating scales), too selective in the literature it quotes (two studies finding more than 20 percent of children and adolescents seen at academic child psychiatry clinics fitting DSM-III criteria for Major Depressive Disorder), and too brief. With these exceptions, this book is a pleasure to read and is instructive to psychiatrists of all persuasions.

ARCHIE A. SILVER, MD
University of South Florida
College of Medicine
Tampa, FL 33612

EMOTIONAL EXPRESSION IN PSYCHOTHERAPY

By Robert Pierce, PhD, Michael Nichols, PhD, and Joyce DuBrin, MA. 287 pp. New York, Gardner Press, 1983. $24.95 (hardcover)

In this volume the authors, three experienced clinical psychologists, set forth the rationale and techniques for a mode of psychotherapy that they consider both innovative and exceptionally effective. Since, in their view, psychotherapy is the consequence of the inadequacy to experience and express emotion, their therapy aims at promoting such expression in a structured, therapeutic setting. Unlike other partisans of expressive therapies, they do not adhere to a naive discharge model, nor are they uncritical adherents of "letting it all hang out." However, they do believe strongly in the value of catharsis which, they say, "does not get rid of feelings; it allows them to be experienced and expressed."

The role of catharsis in psychotherapy is an old issue. Since Breuer and Freud first developed their "talking cure," there have been pendular swings within psychoanalysis and among the practitioners of therapies derived from it between more cognitive and more emotive emphases. The authors err, I believe, in attributing to psychoanalysis a focus on thinking rather than feeling and an interest in intellectual insight; most analysts would regard such intellectualization as resistance against true emotional insight. These authors place themselves in the tradition of Wilhelm Reich and his followers with their emphasis on undoing rigid control mechanisms that prevent the full emergence of appropriate affective responses. At the same time they are critical of those "pop" therapists such as Janov, who seek to abolish thought, reflection and cognitive-affective integration from the therapeutic arena, and of the doctrinaire behaviorists for whom affect is an epiphenomenon.

The therapy described here is an active, strongly directive one, that rejects the analytic model of therapeutic neutrality in favor of the use of warmth, friendliness, role playing, humor and limited physical contact. A strong case is made for the value of hugging, holding and other physical manipulations; the authors seem unaware of Ferenczi's attempt to introduce such measures into psychoanalysis 60 years ago, although they do caution against countertransferential exploitation of such devices.

Several cases are described in considerable detail—enough to give the flavor of the rather informal, yet thoughtful style in which the work is conducted. One senses that, despite the manipulativeness and the use of such concrete devices as rubber baseball bats and pillow pounding to promote expression, an intelligent effort is made to foster both consciousness of repressed affect and its integration into the patient's understanding of his developmental failures. At the same time the authors recognize the extent to which every psychotherapy is an acculturative process, in which the patient is led to take on a system of beliefs and values that, to a significant degree, influences his behavior in therapy and the kinds of "material" he produces. Thus, Kleinian patients report Kleinian dreams, Freudian patients report Oedipal fantasies, and archetypes emerge from the collective unconscious of Jungian patients. This is a book less for the practicing physician than for the trained therapist or student of psychotherapy who wishes to read a responsible presentation of this sort of approach. There is also a scholarly, though inconclusive chapter on research in psychotherapy in general and on cathartic therapies in particular.

AARON ESMAN, MD
The New York Hospital-
Cornell Medical Center
New York, NY 10021

CLINICAL GASTROENTEROLOGY

By Howard M. Spiro, MD. Third edition. 1,549 pp, illustrated. New York, Macmillan Publishing Co, 1983. $88.

In reviewing the third edition of *Clinical Gastroenterology* by Dr Howard Spiro, let me state at the outset that I recommend it wholeheartedly and without reservation as an excellent text and reference book. But more than that, it is quite readable. I particularly enjoyed his anecdotal commentaries, finding them both informative and entertaining.

The text is organized into 11 units, commencing with the esophagus and voyaging down the alimentary tract to the anus. Each of these units is further divided into General Considerations, Congenital Lesions, Infectious Motor Abnormalities, Structural Disorders, Inflammatory Disorders, and, finally, Tumors. Special attention is given to specific common problems such as duodenal and gastric ulcers and the various inflammatory bowel diseases.

Unit Eight skips to the biliary system, the pancreas, and liver. The final unit is a potpourri of less common, but interesting disorders which reflect the author's 28 years of consultation experience. The book is sprinkled with excellent photographs, x-rays, and diagrams. At the conclusion of each chapter, the author provides us with an extensive, well-balanced, and up-to-the-minute bibliography.

Certainly, one cannot agree with every bias that is expressed, but at no time did

I have the impression that the author was pontificating "ex cathedra," but rather drawing on a vast experience that might be obtainable only in a clinical setting at a major teaching institution, in this case, Yale University.

The author has written a thorough text that gets to the core of clinical gastroenterology. It is a book that is invaluable to the physician in the "trenches" of medical practice and one that is readable as well.

JOEL M. INGEGNO, MD
Vassar Brothers Hospital
Poughkeepsie, NY 12601

CRITICAL CARE NURSING HANDBOOK

Compiled and edited by Joan M Joyce, RN, EdD, 274 pp, illustrated. Norwalk, CT, Appleton-Century-Crofts, 1983. $27.50.

This handbook is a learning tool for nurses caring for patients who require critical care nursing. A practical reference with a unified framework, it can be used as an ancillary text for the professional nurse who practices or teaches critical care nursing. The text takes a holistic approach to the adult patient. This handbook is not comprehensive in scope, nor does it offer a succinct definition of critical care nursing or related terms, as a frame of reference is not offered; but it is presented within the context of the nursing process. The text emphasizes assessment and management of the most common clinical conditions of critically ill patients that require priority setting, and recommends a systems approach for evaluation.

The introductory chapter covers the psychological needs of critically ill patients and provides the groundwork for understanding the impact of illness upon patients and families and the problems discussed in following chapters of the text. The unique psychological needs of patients, as related to the most common physiological entities, are limited, and subsequent chapters could benefit from including these needs and appropriate responses, thus providing a reinforcing learning experience. Unfortunately, the impact of critical illness upon the nurse and other health team members is omitted in the handbook.

In succeeding chapters, a review of relevant physiology and pathophysiology offers an overview of normal function and provides an understanding of the deviations from normal. Selected chapters focus on critically ill patients with respiratory, cardiac, renal, neurological and gastrointestinal problems, and burns. A major portion of the book places emphasis on the critically ill patient with respiratory and cardiac problems. Practice tracing questions and answers for calculation and interpretation of electrical axis are an interesting feature of the chapter on cardiac problems.

The nursing care interventions recommended for assessment and management of the critically ill patient are goal-oriented and based on accepted scientific principles and rationale. The recommendations vary from global to specific, but can be adapted to critical care units that have standardized and specific policies and procedures for the care of these special patients.

All of the contributors to the handbook are directly involved in nursing education or practice and present the material with a sense of philosophical and theoretical cohesiveness and continuity. The authors provide helpful and pragmatic information toward achieving increased professional nurse competency in caring for the critically ill patient.

Valuable suggested readings and references and a bibliography are included with each chapter. The reader is cautioned however, that errors exist in the references and that the specificity and clarity of text illustrations are of limited quality.

Overall, *Critical Care Nursing Handbook* is a text that can be useful to nurses responsible for delivering personalized holistic care to the critically ill patient in an acute or long-term setting. Selected parameters for nursing interventions can be extrapolated and modified for application to patients in ambulatory or community settings.

ELIZABETH GLOSS, RN, EdD
States University of New York
Downstate Medical Center
New York, NY 11203

EVOLUTION OF THE DEPARTMENT OF OBSTETRICS AND GYNECOLOGY AT DOWNSTATE 1860–1980

By Leon C. Chesley, PhD. 96 pp. New York, 1983.

The Departments of Obstetrics and Gynecology at the Downstate Medical Center and its predecessor institution, The Long Island College of Medicine, have had a long and illustrious history. Leon C. Chesley has produced in this volume a lively, interesting and succinct overview of the department's history, spanning a 120-year period.

As occurred in many other medical schools, obstetrics, gynecology and diseases of children were merged, separated and recombined at various intervals. In 1899 obstetrics and gynecology came together at the Long Island College of Medicine as one department and have remained so to this day. Chesley traces the history of the department from its early beginnings under James Trask (1860–1863) to its current status under Richard H. Schwarz (1978–present).

The pages of this brief history are filled with a who's who of obstetrics and gynecology: Edwin Chapman, Edward Dunster, the famous Alexander Skene who was chairman from 1870 to 1899 and who also served as dean and president of the Long Island College of Medicine, John Rushmore, John Osborn Polak, Alfred Beck, Charles Gordon, Louis M. Hellman, who chaired the department from 1950 through 1970 and who edited *Williams' Obstetrics*, J. Edward Hall, Schuyler G. Kohl, Edward Solomons and many others.

The department recruited and retained superb faculty who were on the cutting edge of research and other advances in the field. They discovered, innovated, designed and field tested many new concepts and ideas. Residents and fellows were trained who later attained national distinction themselves, bringing much deserved honor to the department. In all of this the author himself played no small part.

The *cognoscenti* will no doubt find oversights of names and events, to be expected in so succinct a history. And there are occasional errors of dates and events. But overall, this book is an extremely interesting and well-written account of a department that has had a consistent and enormous influence on obstetrics and gynecology in the United States. As such the book has broad appeal to all obstetricians and gynecologists as well as to medical historians and other physicians interested in the history of excellence in medical care, research and training in the United States. It is written in an easy-to-read style, merging facts with anecdote. It is hoped Chesley will expand this initial effort into a much larger volume so as to provide us with a more detailed account of this remarkable success story in American medicine.

PASCAL JAMES IMPERATO, MD
Deputy Editor

BOOKS RECEIVED

ALLERGY

Airborne and Allergenic Pollen of North America. By Walter H. Lewis, Prathibha Vinay, Vincent E. Zenger. 254 pp, illustrated. Baltimore, The Johns Hopkins Press, 1983. $60.00 (hardcover).

CARDIOLOGY

An Atlas of Clinical Echocardiography. By Jamie Weir and Ronald Blackwood Pridie. 258 pp, illustrated. Maryland, Urban & Schwarzenberg, 1984. $59.00 (hardcover).

Progress In Cardiology. Edited by Paul N. Yu, MD, John F. Goodwin, MD. 290 pp. Philadelphia, PA, Lea & Febiger, 1983. $45.00 (hardcover).

INTERNAL MEDICINE

Ambulatory Medicine. Edited by Barry Stimmel, MD. 323 pp, illustrated. New York, William Morrow and Company, 1983. $13.95 (hardcover).

LEGAL

Cannibalism and the Common Law. By A. W. Brian Simpson. 353 pp. Illinois, The University of Chicago Press, 1984. $25.00 (clothcover).

It's Easy To Avoid Probate. By Barbara R. Stock. 217 pp. Florida, Linch Publishing, 1983. $16.95 (softcover).

Testifying In Court. By Jack E. Horsley, JD, John Carlova. 154 pp. New Jersey, Medical Economics Company, 1983. $22.95 (hardcover).

MISCELLANEOUS

Alive and Well Naturally. By W. Clarke Blauer. 192 pp. New York, Bantam Books, 1984. $2.95 (softcover).

A Private Practice. By Patrick Reilly, MD. 346 pp. New York, Maomillan Publishing Co, 1984. $15.95 (hardcover).

The Medical Wars: Why the Doctors Disagree. By Rodger Pirnie Doyle. 272 pp, illustrated. New York, William Morrow and Company, 1983. $13.95 (hardcover).

NEUROLOGY

Merritt's Textbook of Neurology. Edited by Lewis P. Rowland, MD. 774 pp, illustrated. Philadelphia, PA, Lea & Febiger, 1984. $48.50 (hardcover).

NUTRITION

Earl Mindell's Pill Bible. By Earl Mindell and Hester Mundis. 384 pp. New York, Bantam Books, 1984. $8.95 (softcover).

ORTHOPEDICS

Beat Backaches. By James Wagenvoord. 63 pp. New York, William Morrow and Company, 1984. $3.95 (softcover).

PATHOLOGY

The Breast. Edited by Robert W. McDivitt, MD, Harold A. Oberman, MD, Luciano Ozzello, MD and Nathan Kaufman, MD. 209 pp, illustrated. Maryland, Waverly Press, Inc., 1984. $45.00 (hardcover).

Practical Diagnosis of Soft Tissue Tumors. By Virginia A. LiVolsi, MD, Maria J. Merino, MD and Michael L. Saruk, MD. 264 pp, illustrated. New Jersey, Medical Economics Company, 1984. $29.95 (hardcover).

PSYCHIATRY

The Addictive Behaviors. By Howard Shaffer, PhD and Barry Stimmel, MD. 172 pp. New York, Haworth Press, Inc, 1984. $22.95 (hardcover).

Beat Insomnia. By James Wagenvoord. 60 pp. New York, William Morrow and Company, 1984. $3.95 (softcover).

Handbook of Emergency Psychiatry. By Nancy Hanke, MD. 262 pp. Massachusetts, D.C. Heath & Co, 1984. $17.95 (softcover).

Management of Chronic Schizophrenia. By Carol L. M. Caton. 210 pp. New York, Oxford University Press, 1984. $19.50 (hardcover).

Transient Psychosis: Diagnosis, Management and Evaluation. Edited by Joe P. Tupin, MD, Uriel Halbbreich, MD and Jesus J. Pena, JD, MPA. 320 pp. New York, Brunner/Mazel Publishing, 1984. $30.00 (hardcover).

SOCIOLOGY

Coping With Childhood Cancer. By David W. Adams, MSW and Eleanor J. Deveau, BScN. Virginia, Reston Publishing Co. 300 pp, illustrated, 1984. $19.95 (hardcover).

Human Behavior in Daily Life. By Leon Merkin, MD. 171 pp. New York, Exposition Press, Inc., 1984. $10.95 (hardcover).

Is It Worth Dying For? By Robert S. Eliot, MD and Dennis L. Breo. 248 pp. New York, Bantam Books, 1984. $14.95 (hardcover).

SURGERY

Varicose Veins Related Diseases and Sclerotherapy: A Guide for Practitioners. By H. I. Feigeleisen. 249 pp, illustrated. Canada, Eden Press, 1984. $35.00 (hardcover).

In addition to these listings, the Journal *will publish obituaries written by physician readers. Inquiries should first be made to the Editor.*

Vincent A. Alaimo MD, Williston Park. Died January 11, 1984; age 51. Dr Alaimo was a 1967 graduate of the Universita Degli Studi di Bologna, Facolta Di Medicina e Chirurgia. He was a member of the Academy of Medicine, the New York State Society of Internal Medicine, the American Society of Nephrology, the Nassau County Medical Society, and the Medical Society of the State of New York.

Leonard M. Aquilino, MD, Syracuse. Died January 12, 1984; age 86. He was a 1925 alumnus of the State University of New York Upstate Medical Center. Dr Aquilino was a Fellow of the American College of Surgeons, and a member of the Academy of Medicine, the Onondaga County Medical Society, and the Medical Society of the State of New York.

Edward I. Braverman, MD, Rockville Centre. Died January 11, 1984; age 50. Dr Braverman was an alumnus of Albert Einstein College of Medicine of Yeshiva University, graduating in 1960. He was a Diplomate of the American Board of Internal Medicine, and a member of the New York State Society of Internal Medicine, the Nassau County Medical Society, and the Medical Society of the State of New York.

Nicholas Joseph Chiara, MD, Brooklyn. Died December 15, 1983; age 69. Dr Chiara graduated in 1941 from the State University of New York Downstate Medical Center. He was a Diplomate of the American Board of Pediatrics, and a member of the American Academy of Pediatrics, the Medical Society of the County of Kings and the Medical Society of the State of New York.

Francis Robert Coyle, MD, Williamsville. Died December 12, 1983; age 76. Dr Coyle was a 1932 graduate of the University of Buffalo School of Medicine. He was a member of the Academy of Medicine, the Medical Society of the County of Erie and the Medical Society of the State of New York.

Gordon Anderson Eadie, MD, Auburn. Died January 5, 1984; age 72. Dr Eadie was a 1938 alumnus of Johns Hopkins University School of Medicine. He was a member of the American Public Health Association, the Medical Society of the County of Cayuga and the Medical Society of the State of New York.

Bruno Fehl, MD, Brooklyn. Died in December 1983; age 82. He was a graduate of Medizinische Fakultat der Universitat, Wien in 1925, and was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Bernardo Marcos Gallego, MD, Cheektowaga. Died December 8, 1983; age 43. He was a 1965 graduate of the University of Santo Tomas Faculty of Medicine and Surgery, Manila. Dr Gallego was a Fellow of the American College of Obstetricians and Gynecologists and a Diplomate of the American Board of Obstetrics and Gynecology. His memberships included the Medical Society of the County of Erie and the Medical Society of the State of New York.

Victor Genco, MD, Sun City Arizona. Died January 5, 1984; age 79. Dr Genco was an alumnus of George Washington University School of Medicine. He graduated in 1929. He was a member of the American Thoracic Society, the Suffolk County Medical Society and the Medical Society of the State of New York.

Louis Gillman, MD, Middletown. Died December 21, 1983; age 63. Dr Gillman was a 1945 graduate of the University of Minnesota Medical School. He was a Diplomate of the American Board of Dermatology and a member of the New York State Dermatological Society, the Medical Society of the County of Orange and the Medical Society of the State of New York.

Samuel Greenstein, MD, New York. Died December 24, 1983; age 97. A 1913 graduate of New York University College of Medicine, Dr Greenstein was a member of the Bronx Medical Society and the Medical Society of the State of New York.

Harvey Hayman, MD, Fayetteville. Died December 24, 1983; age 51. Dr Hayman graduated in 1958 from the State University of New York Upstate Medical Center. He was a member of the Onondaga County Medical Society and the Medical Society of the State of New York.

Arthur Carleton Heist, MD, Westfield. Died January 13, 1984; age 77. Dr Heist was a 1930 alumnus of the University of Buffalo School of Medicine. He was a Fellow of the American College of Angiology, a Qualified Fellow of the International College of Surgeons, and a member of the Medical Society of the County of Chautauqua and the Medical Society of the State of New York.

Milton D. Klein, MD, White Plains. Died January 13, 1984; age 76. Dr Klein was a graduate of George Washington University School of Medicine in 1932. He was a Fellow of the American College of Obstetricians and Gynecologists, the American College of Surgeons, a Qualified Fellow of the International College of Surgeons, a Diplomate of the American Board of Obstetrics and Gynecology, and a member of the Academy of Medicine, the Bronx County Medical Society and the Medical Society of the State of New York.

Frank LaGattuta, MD, Bronx. Died January 17, 1984; age 88. Dr LaGattuta was an alumnus of Fordham University School of Medicine, graduating in 1920.

He was a Diplomate of the American Board of Ophthalmology, a Qualified Fellow of the International College of Surgeons, a Fellow of the American College of Surgeons, and a member of the American Academy of Ophthalmology and Otolaryngology, the Bronx County Medical Society, and the Medical Society of the State of New York.

Marion D. Laird, MD, New York. Died November 18, 1983; age 82. Dr Laird graduated in 1928 from the University of Toronto Faculty of Medicine. He was a Fellow of the American College of Obstetricians and Gynecologists, and a Diplomate of the American Board of Obstetrics and Gynecology. He was a member of the New York County Medical Society and the Medical Society of the State of New York.

Jesse Marcus Levitt, MD, Brooklyn. Died October 5, 1983; age 78. Dr Levitt was a 1927 alumnus of the State University of New York Downstate Medical Center. He was a Fellow of the American College of Surgeons and a Diplomate of the American Board of Ophthalmology. His memberships included the Academy of Medicine, the New York Society for Clinical Ophthalmology, the American Academy of Ophthalmology and Otolaryngology, the Pan American Association of Ophthalmology, the Medical Society of the County of Kings and the Medical Society of the State of New York.

Norman Campbell Lyster, MD, Norwich. Died January 23, 1984; age 78. Dr Lyster attended McGill University Faculty of Medicine, graduating in 1930. He was a member of the Chenango County Medical Society and the Medical Society of the State of New York.

Ambrose A. Macie, MD, Buffalo. Died December 28, 1983; age 59. Dr Macie graduated in 1950 from Marquette University School of Medicine. He was a Fellow of the American College of Obstetricians and Gynecologists, a Diplomate of the American Board of Obstetrics and Gynecology, and a member of the Pan American Medical Association, the Medical Society of the County of Erie, and the Medical Society of the State of New York.

Adolph Neustadt, MD, Bronx. Died November 3, 1983; age 91. Dr Neustadt was a 1918 graduate of Friedrich-Wilhelms-Universitat Medical Fakultat, Berlin, Prussia. He was a member of the Bronx County Medical Society and the Medical Society of the State of New York.

Paul Van Dyne Newland, MD, Norwich. Died December 26, 1983; age 76. A 1935 graduate of the University of Rochester School of Medicine and Dentistry, Dr Newland was a Fellow of the American College of Physicians. His memberships included the American Geriatrics Society, the American Occupational Medical Association, the Medical Society of the County of Chenango, and the Medical Society of the State of New York.

Leman Winfred Potter, MD, Newark. Died January 1, 1984; age 70. Dr Potter attended New York Medical College, Flower and Fifth Avenue Hospitals, graduating in 1940. He was a Diplomate of the American Board of Family Practice, and a Fellow of the American Academy of Family Practice. His memberships included the Medical Society of the County of Wayne and the Medical Society of the State of New York.

Eugene Raicus, MD, Neponsit. Died October 2, 1983; age 66. A 1944 graduate of the Chicago Medical School, Dr Raicus was a Fellow of the American College of Angiology, a Qualified Fellow of the International College of Surgeons, and a member of the American Society of Abdominal Surgeons, the Medical Society of the County of Kings and the Medical Society of the State of New York.

John Raphael Roche, MD, Roslyn Heights. Died January 25, 1984. An alumnus of Georgetown University School of Medicine, Dr Roche graduated in 1936. He was a Fellow of the American College of Surgeons and a Diplomate of the American Board of Ophthalmology. His memberships included the American Academy of Ophthalmology and Otolaryngology, the Nassau County Medical Society and the Medical Society of the State of New York.

Nat Schlossman, MD, Brooklyn. Died January 4, 1984; age 85. Dr Schlossman was a 1923 alumnus of New York University College of Medicine. He was a member of the American Academy of Family Practice, the Medical Society of the County of Kings and the Medical Society of the State of New York.

Eugene Joseph Smith, MD, Breezy Point. Died June 26, 1983; age 67. He was an alumnus of the State University of New York Downstate Medical Center, graduating in 1943. His memberships included the New York Cardiological Society, the American Academy of Family Practice, the American Geriatrics Society, the Medical Society of the County of Kings and the Medical Society of the State of New York.

Herbert Ignaz Spitzel, MD, White Plains. Died December 26, 1983; age 87. Dr Spitzel was an alumnus of Hamburgische Universitat Medizinische Fakultat, Hamburg, graduating in 1920. He was a Diplomate of the American Board of Obstetrics and Gynecology, and his memberships included the Clinical Society of the New York Diabetes Association, the Medical Society of the County of Westchester and the Medical Society of the State of New York.

Robert Ellis Storms, MD, Westfield. Died November 27, 1983; age 69. He graduated in 1939 from the University of Buffalo School of Medicine. Dr Storms was a Fellow of the American Academy of Family Practice, and a member of the American Academy of Allergy, the Medical Society of the County of Chautauqua and the Medical Society of the State of New York.

Charles William K. Tomlinson, MD, Amsterdam. Died January 13, 1984; age 91. He was a 1915 graduate of Albany Medical College of Union University. Dr Tomlinson was a member of the Radiological Society of New York State, the Medical Society of the County of Montgomery and the Medical Society of the State of New York.

Paul Krim Woodrow, MD, Englewood, New Jersey. Died November 14, 1983; age 49. Dr Woodrow was a 1959 graduate of the New York Medical College, Flower and Fifth Avenue Hospitals. He was a Diplomate of the American Board of Radiology, and a member of the Radiological Society of New York State, the Medical Society of the County of Kings and the Medical Society of the State of New York.

Irving A. Zimmerman, MD, Brooklyn. Died November 20, 1983; age 71. A 1938 alumnus of the State University of New York Downstate Medical Center, he was a Diplomate of the American Board of Internal Medicine and a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Guidelines for authors

ORIGINALITY

The *New York State Journal of Medicine* welcomes research papers and original essays on the practice of medicine, medical education, public health, the history of medicine, medicolegal matters, legislation, ethics, the mass media and socioeconomic issues in health care.

Manuscripts should be prepared according to the "Uniform requirements for manuscripts submitted to biomedical journals" (*NY State J Med* 1983; 83:1089-1094). The requirements were established by the International Committee of Medical Journal Editors, of which the *Journal* is a participating member. These Guidelines are intended to highlight aspects of the *Journal*'s particular style of publication.

A manuscript will be considered for publication if it is original, has not been published previously in whole or in part in either a medical journal or a lay publication, and is not simultaneously under consideration elsewhere. A copy of any possibly duplicative material, such as a reference "in press," should be submitted along with the manuscript.

PREPARATION

An original typewritten or "word-processed" manuscript and two photocopies (to facilitate outside review) are required. If the manuscript is not accepted for publication, the original and one copy will be returned. All figures must be submitted in triplicate. The manuscript should be double-spaced throughout, including references, tables, legends, quotations, and acknowledgments. A separate title page should include the full title of the paper in upper and lower case type, the names of the authors exactly as they should appear in print (including their highest academic degree), an abbreviated title of no greater than 40 spaces for use as a running foot, and the names of all providers of funding for research on which the paper is based. Information on the amount and allocation of funding is optional.

A corresponding author should be designated in the covering letter. Authors should list their title and affiliation at the time they did the work, and, if different, their present affiliation. The addresses and telephone numbers of all authors should be supplied for editorial purposes. All authors of a manuscript are responsible for having read and approved it for submission.

CATEGORIES

Research Papers should be limited to 2,500 words and should include the following sections: Introduction, Methods, Results, Discussion, and References. Multiple subheadings and numbered lists are discouraged. An abstract limited to 150 words should state the reasons for the study, the main findings, and their implications. Statistical evaluations should be described in the Methods section, and the name and affiliation of the statistician should be included in the acknowledgments if this individual is not listed as a coauthor. Reports of experiments involving human subjects must include a description in the Methods section of the informed consent obtained and a statement that the procedures followed were approved by an institutional research review committee. Anonymity of patients must be preserved. Reports of experiments on animals must note which guidelines were followed for the care and use of laboratory animals.

Case Reports should be limited to 1,250 words. Review Articles should not exceed 3,000 words. Commentaries should be between 750 and 1,000 words. Other kinds of original essays should not exceed 2,000 words. A letter of inquiry should be sent to the editor prior to submitting a Review Article or Commentary.

For Research Papers only, scientific measurements should be given in conventional units, with Système Internationale (SI) units in parentheses. Abbreviations and acronyms should be kept to a minimum, and jargon should be avoided. Generic names of drugs should be used instead of brand names.

FIGURES

The submission of color illustrations or slides is discouraged. Only black and white glossy photographic prints or "camera-ready" artwork will be accepted. The *Journal* is unable to provide art services such as the addition of arrows to photographs. A signed consent for publication must accompany photographs in which the patient is identifiable. Illustrations from other publications generally will not be considered. Legends for illustrations should be typed on a separate sheet, and for photomicrographs should include magnification and stain. Each illustration should be lightly marked on the back in pencil with the name of the first author, the number as cited in the text, and an arrow indicating the top. Each set of illustrations should be submitted unmounted in a separate envelope.

Tables should be simple, self-explanatory, and few in number. Each table should be typed double-spaced on a separate sheet.

REFERENCES

References should be limited to the most pertinent. The recommended maximum number of references is 25 for Research Papers and most other original contributions (except lengthier Review Articles), 12 for Commentaries and Case Reports, and six for letters to the editor.

Authors are responsible for the accurate citation of references. Citation of secondary sources is discouraged except where the original reference is unobtainable. Authors may not cite references they have not read, and the use of abstracts as references should be avoided.

References should be indicated in the text by superscript numbers following the name of the author (eg, Smith^2 reported two cases).

The list of references at the end of the article should be typed double-spaced and references should be numbered in the order in which they appear on the text. When there are six or fewer authors, all should be listed; where there are seven or more, the first three should be listed, followed by *et al.* Names of journals should be abbreviated according to *Index Medicus* and underlined.

Sample references:

1. Kepes ER, Thomas P, Vemulapalli K: Methadone and intravenous morphine requirements. *NY State J Med* 1983; 83:925-927.
2. McGuigan JE. Peptic ulcer. In: Petersdorf RG, Adams RD, Braunwald E, Isselbacher KJ, Martin JB, Wilson JD, eds. *Harrison's Principles of Internal Medicine*. New York, McGraw-Hill, 1983, pp 1697-1712.

REVIEW

All manuscripts are reviewed by the editors, and most manuscripts are sent to outside referees. Decisions concerning acceptance, revision, or rejection of a manuscript are usually made within three to six weeks. Every effort will be made to assure prompt publication of an accepted manuscript. A galley proof will be sent to the author for approval prior to publication.

Address correspondence to Alan Blum, MD, Editor, *New York State Journal of Medicine*, P.O. Box 5404, 420 Lakeville Road, Lake Success, NY 11042.

The definitive analysis of the world cigarette pandemic

NEW YORK STATE JOURNAL OF MEDICINE
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COLUMBIA JOURNALISM REVIEW

An extra press run has enabled the NEW YORK STATE JOURNAL OF MEDICINE to offer single or bulk copies of its recent issue on the world cigarette pandemic. As the official publication of the Medical Society of the State of New York since 1900, the *Journal* is one of the foremost independent peer-reviewed general medical journals in the country. Providing timely and stimulating commentary, challenging research papers, analysis of clinical trends, debate on topical issues, and in-depth coverage of medical news, the *Journal* makes important reading—and a welcome gift—to physicians and students in the United States or abroad. A free copy of the December issue will be included with each subscription.

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MEETINGS AND LECTURES

The New York State Journal of Medicine *cannot guarantee publication of meetings and lectures unless the information is submitted at least two months prior to the event.*

JULY 1984

AROUND THE STATE

SCHENECTADY

July 6-7. **Genetics and the Human Encounter with Alcohol.** Info: Office of Graduate and Continuing Studies, Union College, One Union Ave, Schenectady, NY 12308. Tel: (518) 370-6288.

SUFFOLK

July 16-20. **Diagnostic Imaging: A 1984 Update.** 15 Cat 1 credits. *July 23-27.* **Anesthesiology Today: Its Relation to the Community.** 15 Cat 1 credits. *July 30-Aug 1.* **Respiratory Failure: New Approaches to Management.** 15 Cat 1 credits. Info: Office of CME, Albert Einstein College of Medicine/Montefiore Medical Center, 111 East 210th Street, Bronx, NY 10467. Tel: (212) 920-6674.

TOMPKINS

July 22-27. **The Diagnosis and Treatment of Non-Psychotic Disorders.** 30 Cat 1 credits. Info: Dr Allen Frances, Director, c/o Programs in Professional Education, B 12 Ives Hall, Cornell University, Ithaca, NY 14853. Tel: (607) 256-4987.

AROUND THE NATION

CALIFORNIA

July 6-8. **International Congress of Chinese Medicine.** Info: Pedro Chan, Center for Chinese Medicine, 230 South Garfield Ave, Ste 202, Monterey Park, CA 91754. Tel: (213) 572-0424.

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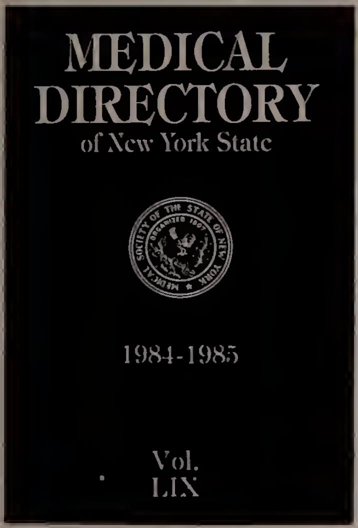

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10/12-10/13	612. Seminar in Ultrasonography
10/13	456. Fine Needle Aspiration of the Prostate Gland
10/15, 17, 22, 24	156. Medical Mycology
10/18-10/21	150. An Eclectic Retrospective: Updated Selections From a Decade of Dermatopathology Symposia at NYU
10/20	550. How to Manage Mental Disorders in General Medical Practice
10/25-10/28	611. Imaging of the Head and Neck (Essex House)
NOVEMBER	
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11/28-11/30	700. Pitfalls in Surgery
DECEMBER	
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12/3-12/7	314. Toxicology and Pharmacology
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9/5-3/13	561. Comprehensive Psychiatry: Review & Recent Advances (Wednesdays 8-10pm)
9/5-12/21	400. Basic Sciences in Ophthalmology
9/12-5/22	420. Basic Sciences in Otolaryngology
1/9-6/19	302. Internal Medicine Board Review
FOR INFORMATION	NYU Post-Graduate Medical School 550 First Avenue, New York, NY 10016 (212)340-5295 (24 hr. service)

July 10–12. **Family Practice Board Review Course, PG.** San Francisco. Info: Univ of California, Extended Programs in Medical Education, 533 Parnassus Ave, U-569, San Francisco, CA 94143.

COLORADO

July 9–13. **20th Annual Internal Medicine Program.** 25 Cat 1 credits. Info: Joanne Bauer, University of Colorado School of Medicine, CME, 4200 E 9th Ave, Box C-295, Denver, CO 80262. Tel: (303) 394-5241.

DELAWARE

July 22–28. **An Intensive Review of Internal Medicine.** 45 Cat 1 credits. Info: Sylvia Brocka, University of Delaware, 2800 Pennsylvania Ave, Wilmington, DE 19806.

DISTRICT OF COLUMBIA

July 29–Aug 3. **American Association for Clinical Chemistry 36th National Meeting.** Info: Deborah Woodcock, AACC Meetings Dept, 1725 K St, NW, Ste 1010, Washington DC 20006. Tel: (202) 857-0717.

GEORGIA

July 27–29. **Allergy and Clinical Immunology for Primary Care Physicians.** Cloisters at Sea Island, GA. Info: Harold Ifft, Executive Director, Association for the Care of Asthma, Box 568, Ossining, NY 10562.

MAINE

July 9–11. **3rd Bar Harbor Medical Symposium: Current Concepts in Clinical Medicine and Pathophysiology.** 14 Cat 1 credits. Info: Joanne Adams Medical Care Development, Inc, 11 Parkwood Dr, August, ME 04330. Tel: (207) 622-7566.

July 31–Aug. 3. **Update in Allergy and Clinical Immunology.** Info: Robert Kany, Director of Special Programs, Colby College, Waterville, ME 04901. Tel: (207) 873-1131.

MASSACHUSETTS

July 2–Sept 7. **Fifth Annual Cape Cod Institute.** Info: Office of Continuing Education, Department of Psychiatry, Albert Einstein College of Medicine, Montefiore Medical Center, 111 East 210th Street, Bronx, NY 10467. Tel: (212) 920-6676.

SOUTH CAROLINA

July 12–14. **Clinical Obstetrics—Recent Advances.** 16 Cat 1 credits. Info: Division of Continuing Education, Medical College of Georgia, Augusta, GA 30912. Tel: (404) 828-3967.

July 26–28. **Genetics for Practitioners.** 17 Cat 1 credits. Info: Division of Continuing Education, Medical College of Georgia, Augusta, GA 30912. Tel: (404) 828-3967.

WYOMING

July 25–29. **Cardiothoracic Imaging—State of the Art.** 22 Cat 1 credits. Info: Judy Gallegos, Dept of Radiology, University of Utah School of Medicine, Salt Lake City, Utah 84132.

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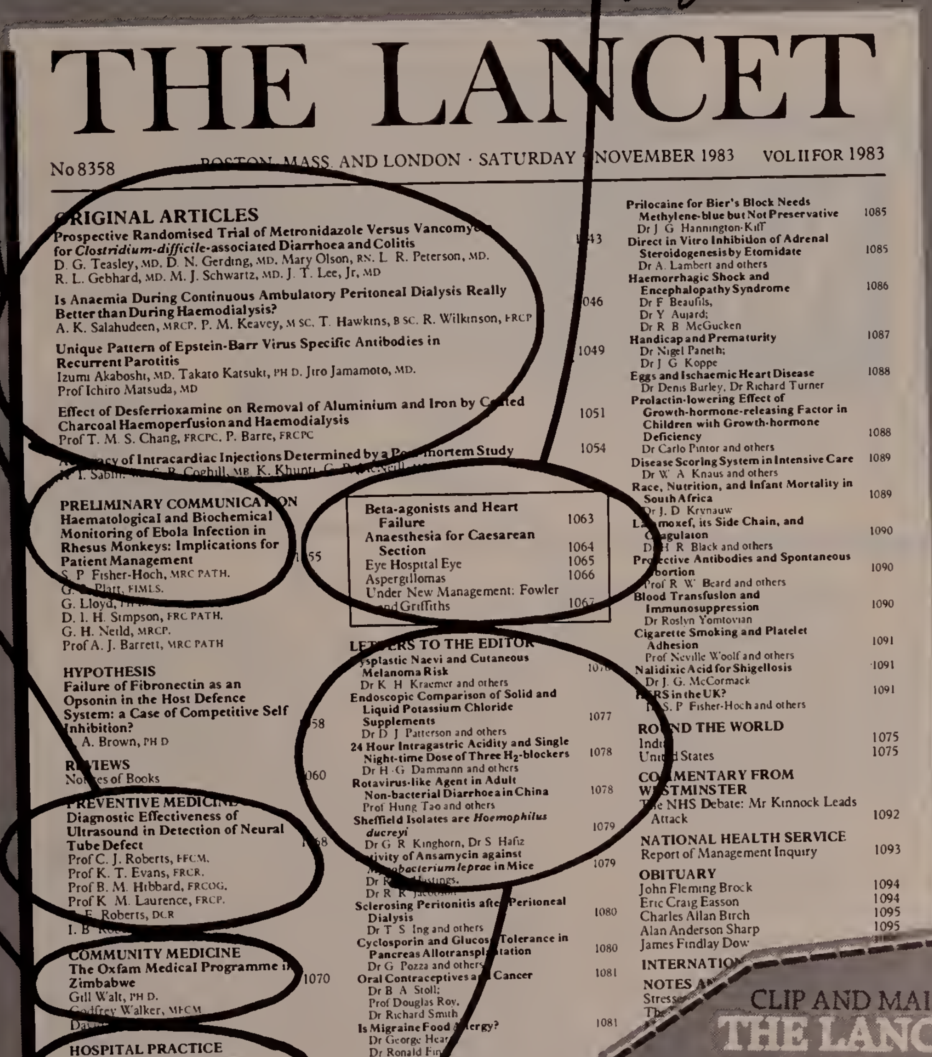

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Gastrointestinal symptoms occur in about 2 5 percent of patients and include diarrhea (1 in 70)

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment Nausea and vomiting have been reported rarely

Hypersensitivity reactions have been reported in about 1 5 percent of patients and include morbilliform eruptions (1 in 100) Pruritus, urticaria and positive Coombs' tests each occur in less than 1 in 200 patients Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever) have been reported These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Ceclor Such reactions have been reported more frequently in children than in adults Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy No serious sequelae have been reported Antihistamines and corticosteroids appear to enhance resolution of the syndrome

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients)

Causal Relationship Uncertain—Transitory abnormalities in clinical laboratory test results have been reported Although they were of uncertain etiology they are listed below to serve as alerting information for the physician

Hepatic—Slight elevations of SGOT, SGPT, or alkaline phosphatase values (1 in 40)

Hematopoietic—Transient fluctuations in leukocyte count predominantly lymphocytosis occurring in infants and young children (1 in 40)

Renal—Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200)

[061782R]

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*Many authorities attribute acute infectious exacerbation of chronic bronchitis to either *S pneumoniae* or *H influenzae* [8]

Note Ceclor is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever See prescribing information

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8 Principles and Practice of Infectious Diseases (edited by G L Mandell, R G Douglas, Jr and J E Bennett), p 487 New York John Wiley & Sons, 1979

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Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46285

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MISCELLANEOUS—CONT'D

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1. Stone PH, Turi ZG, Muller JE: Efficacy of nifedipine therapy for refractory angina pectoris. *Am Heart J* 104:672-681, September 1982.
2. Antman E, Muller J, Goldberg S, et al: Nifedipine therapy for coronary-artery spasm: Experience in 127 patients. *N Engl J Med* 302:1269-1273, June 5, 1980.

BRIEF SUMMARY
PROCARDIA® (nifedipine) **CAPSULES** For Oral Use

INDICATIONS AND USAGE: I. Vasospastic Angina: PROCARDIA (nifedipine) is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. PROCARDIA may also be used where the clinical presentation suggests a possible vasospastic component but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina): PROCARDIA is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in those patients are incomplete.

Controlled studies in small numbers of patients suggest concomitant use of PROCARDIA and beta blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely since severe hypotension can occur from the combined effects of the drugs. (See Warnings.)

CONTRAINDICATIONS: Known hypersensitivity reaction to PROCARDIA.

WARNINGS: Excessive Hypotension: Although in most patients, the hypotensive effect of PROCARDIA is modest and well tolerated, occasional patients have had excessive and poorly tolerated hypotension. These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers.

Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving PROCARDIA together with a beta blocking agent who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of PROCARDIA and a beta blocker, but the possibility that it may occur with PROCARDIA alone, with low doses of fentanyl, in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In PROCARDIA treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and, if the patient's condition permits, sufficient time (at least 36 hours) should be allowed for PROCARDIA to be washed out of the body prior to surgery.

Increased Angina: Occasional patients have developed well documented increased frequency, duration or severity of angina on starting PROCARDIA or at the time of dosage increases. The mechanism of this response is not established but could result from decreased coronary perfusion associated with decreased diastolic pressure with increased heart rate, or from increased demand resulting from increased heart rate alone.

Beta Blocker Withdrawal: Patients recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of PROCARDIA treatment will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and PROCARDIA initiation. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning PROCARDIA.

Congestive Heart Failure: Rarely, patients, usually receiving a beta blocker, have developed heart failure after beginning PROCARDIA. Patients with tight aortic stenosis may be at greater risk for such an event.

PRECAUTIONS: General: Hypotension: Because PROCARDIA decreases peripheral vascular resistance, careful monitoring of blood pressure during the initial administration and titration of PROCARDIA is suggested. Close observation is especially recommended for patients already taking medications that are known to lower blood pressure. (See Warnings.)

Peripheral edema: Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, occurs in about one in ten patients treated with PROCARDIA. This edema occurs primarily in the lower extremities and usually responds to diuretic therapy. With patients whose angina is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction.

Drug Interactions: Beta-adrenergic blocking agents: (See Indications and Warnings.) Experience in over 1400 patients in a non-comparative clinical trial has shown that concomitant administration of PROCARDIA and beta-blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension or exacerbation of angina.

Long-acting nitrates: PROCARDIA may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.

Digitalis: Administration of PROCARDIA with digoxin increased digoxin levels in nine of twelve normal volunteers. The average increase was 45%. Another investigator found no increase in digoxin levels in thirteen patients with coronary artery disease. In an uncontrolled study of over two hundred patients with congestive heart failure during which digoxin blood levels were not measured, digitalis toxicity was not observed. Since there have been isolated reports of patients with elevated digoxin levels, it is recommended that digoxin levels be monitored when initiating, adjusting, and discontinuing PROCARDIA to avoid possible over- or under-digitalization.

Carcinogenesis, mutagenesis, impairment of fertility: When given to rats prior to mating, nifedipine caused reduced fertility at a dose approximately 30 times the maximum recommended human dose

Pregnancy: Category C. Please see full prescribing information with reference to teratogenicity in rats, embryotoxicity in rats, mice and rabbits, and abnormalities in monkeys.

ADVERSE REACTIONS: The most common adverse events include dizziness or light-headedness, peripheral edema, nausea, weakness, headache and flushing each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%. Syncopal episodes did not recur with reduction in the dose of PROCARDIA or concomitant antianginal medication. Additionally, the following have been reported: muscle cramps, nervousness, dyspnea, nasal and chest congestion, diarrhea, constipation, inflammation, joint stiffness, shakiness, sleep disturbances, blurred vision, difficulties in balance, dermatitis, pruritus, urticaria, fever, sweating, chills, and sexual difficulties. Very rarely, introduction of PROCARDIA therapy was associated with an increase in anginal pain, possibly due to associated hypotension.

In addition, more serious adverse events were observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. Myocardial infarction occurred in about 4% of patients and congestive heart failure or pulmonary edema in about 2%. Ventricular arrhythmias or conduction disturbances each occurred in fewer than 0.5% of patients.

Laboratory Tests: Rare, mild to moderate, transient elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT, and SGPT have been noted, and a single incident of significantly elevated transaminases and alkaline phosphatase was seen in a patient with a history of gall bladder disease after about eleven months of nifedipine therapy. The relationship to PROCARDIA therapy is uncertain. These laboratory abnormalities have rarely been associated with clinical symptoms Cholestasis, possibly due to PROCARDIA therapy, has been reported twice in the extensive world literature.

HOW SUPPLIED: Each orange, soft gelatin PROCARDIA CAPSULE contains 10 mg of nifedipine PROCARDIA CAPSULES are supplied in bottles of 100 (NDC 0069-2600-66), 300 (NDC 0069-2600-72), and unit dose (10x10) (NDC 0069-2600-41). The capsules should be protected from light and moisture and stored at controlled room temperature 59° to 77°F (15° to 25°C) in the manufacturer's original container.

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Quotes from an unsolicited letter received by Pfizer from an angina patient.
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"My daily routine consisted of sitting in my chair trying to stay alive."

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PROCARDIA can mean the return to a more normal life for your patients—having fewer anginal attacks,[1] taking fewer nitroglycerin tablets,[2] doing more, and being more productive once again.

Side effects are usually mild (most frequently reported are dizziness or lightheadedness, peripheral edema, nausea, weakness, headache and flushing, each occurring in about 10% of patients, transient hypotension in about 5%, palpitation in about 2% and syncope in about 0.5%).

for the varied faces of angina

PROCARDIA®
(NIFEDIPINE) *Capsules 10 mg*

*Procardia is indicated for the management of:
1) Confirmed vasospastic angina.
2) Angina where the clinical presentation suggests a possible vasospastic component.
3) Chronic stable angina without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or nitrates or who cannot tolerate these agents. In chronic stable angina (effort-associated angina) PROCARDIA has been effective in controlled trials of up to eight weeks' duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients are incomplete.

Please see PROCARDIA *brief summary on adjoining page.*

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Unlike calcium blockers, INDERAL LA—either alone or with a nitrate—is recommended for early treatment of angina in the majority of patients. Equally important, INDERAL LA delivers the proven performance and safety profile of INDERAL tablets—confirmed by millions of patients during 16 years of clinical use.

START WITH 80 MG ONCE DAILY

Dosage may be increased to 160 mg once daily, as needed, to achieve optimal control. INDERAL LA should not be used in congestive heart failure, sinus bradycardia, cardiogenic shock, heart block greater than first degree, and bronchial asthma. Please see next page for further details and brief summary of prescribing information.

ONCE-DAILY **INDERAL LA**

(PROPRANOLOL HCl) *LONG ACTING CAPSULES*

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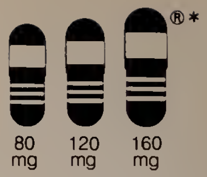

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)*
INDERAL* LA brand of propranolol hydrochloride **(Long Acting Capsules)**
DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.
CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period

The mechanism of the antihypertensive effect of INDERAL has not been established Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential The significance of the membrane action in the treatment of arrhythmias is uncertain

The mechanism of the antimigraine effect of propranolol has not been established Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain.

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable
INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension, it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation Clinical improvement may be temporary
CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL
WARNINGS. CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible)

> IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)— PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e g , dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers

DIABETES AND HYPOGLYCEMIA: Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm Propranolol does not distort thyroid function tests

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker In one case this resulted after an initial dose of 5 mg propranolol
PRECAUTIONS. *General:* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies

Beta adrenoreceptor blockade can cause reduction of intraocular pressure Patients should be told that INDERAL may interfere with the glaucoma screening test Withdrawal may lead to a return of increased intraocular pressure

Clinical Laboratory Tests Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity There were no drug-related tumorigenic effects at any of the dosage levels Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug

Pregnancy. Pregnancy Category C INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Nursing Mothers: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman

Pediatric Use: Safety and effectiveness in children have not been established
ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia, congestive heart failure; intensification of AV block, hypotension, paresthesia of hands; thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System. lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia, visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics

Gastrointestinal. nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress

Respiratory: bronchospasm.

Hematologic. agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Auto-Immune. In extremely rare instances, systemic lupus erythematosus has been reported

Miscellaneous. alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol
DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained INDERAL LA should not be considered a simple mg for mg substitute for INDERAL INDERAL LA has different kinetics and produces lower blood levels Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval

HYPERTENSION—*Dosage must be individualized* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved The usual maintenance dosage is 120 to 160 mg once daily In some instances a dosage of 640 mg may be required The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks

ANGINA PECTORIS—*Dosage must be individualized* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS)

MIGRAINE—*Dosage must be individualized* The initial oral dose is 80 mg INDERAL LA once daily The usual effective dose range is 160-240 mg once daily The dosage may be increased gradually to achieve optimum migraine prophylaxis If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued It may be advisable to withdraw the drug gradually over a period of several weeks

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily

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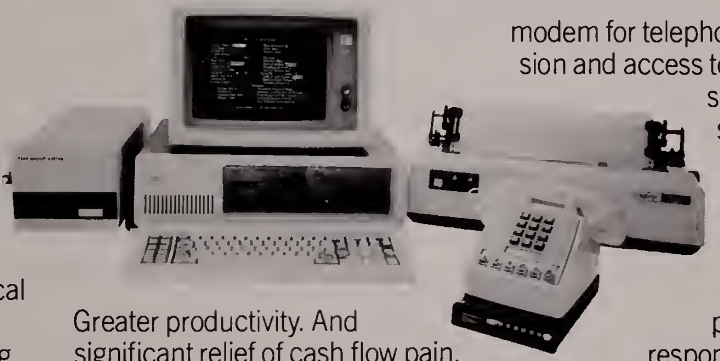

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This issue of the Journal *consists of papers presented at the March 13, 1984 symposium, "New York State and the Offshore Medical Schools," co-sponsored by the Department of Preventive Medicine and Community Health, Downstate Medical Center and the* New York State Journal of Medicine. *These papers address numerous current and relevant issues concerning offshore medical schools, their students and graduates.*

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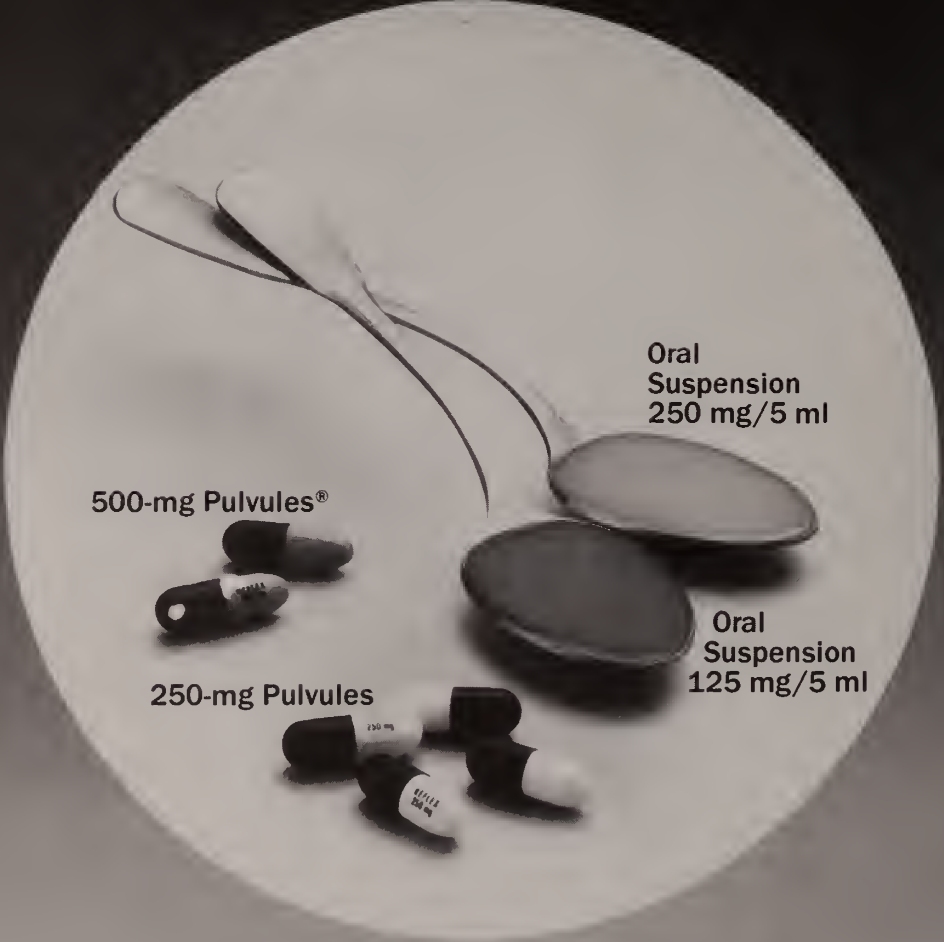

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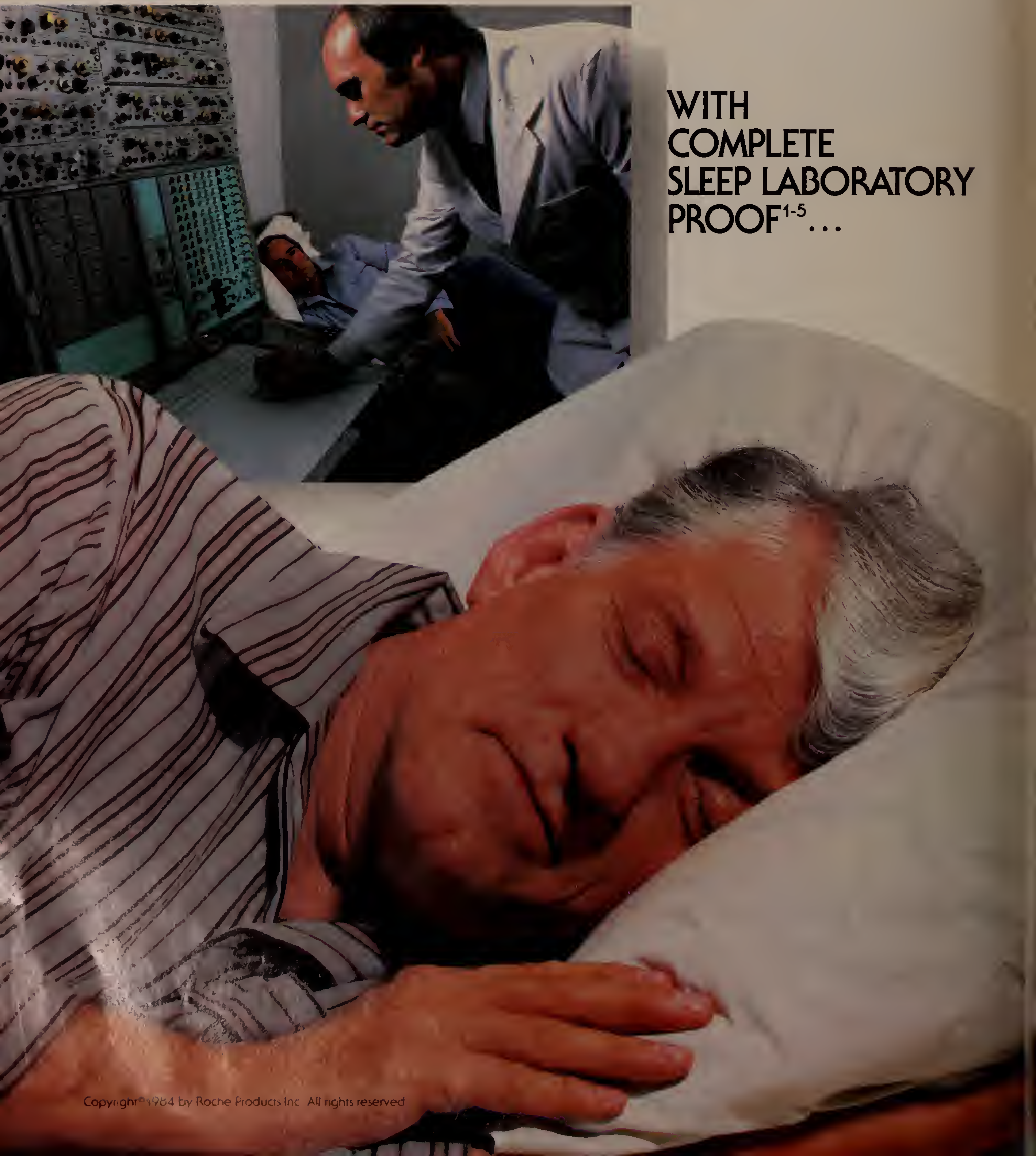

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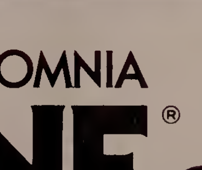

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Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins, and alkaline phosphatase; and paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity.

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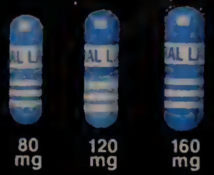

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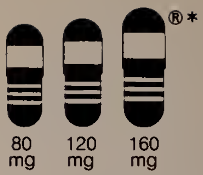

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DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.
CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity.

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain.

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension, it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS. CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

> IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY. The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g. dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. *General:* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block, hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized.* The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily.

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

*The appearance of INDERAL LA capsules is a registered trademark of Ayerst Laboratories.
8833/384

Ayerst. AYERST LABORATORIES
New York, N.Y. 10017

BALANCED CALCIUM CHANNEL BLOCKADE!

CARDIZEM®
(diltiazem HCl)
balances potent coronary vasodilation with a low incidence of side effects

Low incidence of side effects
CARDIZEM® (diltiazem HCl) produces an incidence of adverse reactions not greater than that reported with placebo therapy, thus contributing to the patient's sense of well-being.

*Cardizem is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

References:

1. Strauss WE, McIntyre KM, Parisi AF, et al: Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris: Report of a cooperative clinical trial. Am J Cardiol 49:560-566, 1982.
2. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. Chest 78 (July suppl):234-238, 1980.

Reduces angina attack frequency*
42% to 46% decrease reported in multicenter study.[1]

Increases exercise tolerance*
In Bruce exercise test,[2] control patients averaged 8.0 minutes to onset of pain; Cardizem patients averaged 9.8 minutes ($P<.005$).

CARDIZEM®
(diltiazem HCl)

THE BALANCED CALCIUM CHANNEL BLOCKER

Please see full prescribing information on following page.

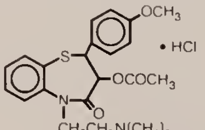
2/84

PROFESSIONAL USE INFORMATION

cardizem®
(diltiazem HCl)
30 mg and 60 mg tablets

DESCRIPTION

CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+)-cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem hydrochloride for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina. CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIONS and ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS).

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%), AV block (1.1%). In addition, the following events were reported infrequently (less than 1%) with the order of presentation corresponding to the relative frequency of occurrence.

Cardiovascular:	Flushing, arrhythmia, hypotension, bradycardia, palpitations, congestive heart failure, syncope.
Nervous System:	Paresthesia, nervousness, somnolence, tremor, insomnia, hallucinations, and amnesia.
Gastrointestinal:	Constipation, dyspepsia, diarrhea, vomiting, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH.
Dermatologic:	Pruritus, petechiae, urticaria, photosensitivity.
Other:	Polyuria, nocturia.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: erythema multiforme; leukopenia; and extreme elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been limited. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral/LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. Although individual patients may respond to any dosage level, the average optimum dosage range appears to be 180 to 240 mg/day. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

Cardizem 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1771-49). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1772-49). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

Issued 4/1/84

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NEW YORK STATE
JOURNAL OF MEDICINE

July 1984 • Volume 84, Number 7

An overview of New York State and the offshore medical schools

PASCAL JAMES IMPERATO, MD

The term "offshore medical school" is a relatively new one that developed during the 1970s. It was initially applied to new medical schools that were established on several Caribbean islands. Over the past few years the term has been extended to include schools in Mexico, the Philippines and Central America.

The Association of American Medical Colleges (AAMC) has referred to the offshore medical schools as foreign chartered schools of medicine operating in the United States.[1] This definition is more accurate than the term offshore medical schools since it includes an important characteristic of these schools, namely the direction of some of their activities from offices within the United States. Of the approximately 1,000 medical schools located outside of the United States and listed by the World Health Organization, fewer than 15 maintain offices in the United States.[1] These schools primarily solicit and enroll American nationals, most of whom have been unsuccessful applicants for positions in medical schools in the United States. Indeed, a number of these schools were developed in response to the perceived needs of these unsuccessful candidates. This is particularly true for many of the schools located on various Caribbean islands, nearly all of whose students are citizens of the United States. Other long-established private universities, such as several in Mexico, also responded to this increased demand for medical education by expanding their classes to accommodate US citizens. They, like the Caribbean schools, are foreign chartered schools of medicine functioning in the United States (Table I).

CHARACTERISTICS OF THE OFFSHORE MEDICAL SCHOOLS

The offshore medical schools are usually private and often proprietary. The Ad Hoc Committee of the AAMC on Foreign-Chartered Medical Schools and US Nationals Studying Medicine Abroad has pointed out that many of these schools heavily depend on visiting teaching faculty from the US and Europe whose pedagogical visits are brief and episodic.[1] Such visits are often "working vacations" for these visiting educators who play no role in curriculum development and frequently no role in student evaluation and promotion. These visitors, however, add luster to the reputations of these schools and are prominently mentioned in promotional literature sent to potential enrollees.

In a number of these schools, attendance at classes in the basic sciences and on campus is not enforced. Not infrequently students have remained in the United States for varying periods, engaged in self-study, returning for examinations. But American medical educators are not in a strong position to criticize this deficiency. Attendance at such classes in American medical schools often runs no greater than 50 percent. Student transcription services tape lectures, transcribe them, and make them available to students for a fee. It should be noted that several instances have been uncovered of such transcripts being sold to US foreign medical students (USFMS), in direct violation of US common and copyright law.

Some offshore medical schools grant advanced standing to applicants who possess training or degrees in other fields such as nursing, podiatry and the medical technologies. They have also given MD degrees to the holders of Doctor of Osteopathy (DO) degrees upon payment of a fee.

Most offshore medical schools are located in geographic areas that do not contain a large enough population to support adequate hospital teaching facilities. Consequently, they have had to turn to contractual arrangements with American hospitals to provide clinical experience for their students. Many of these arrangements are made with hospitals that do not have approved residency programs. Of greater concern is the practice of certain schools of awarding academic credit to students for making their own clinical rotation arrangements. Some of these have consisted

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Address correspondence to Dr Imperato, Professor and Chairman, Dept of Preventive Medicine and Community Health, State University of New York, Downstate Medical Center, Brooklyn, NY 11203.

TABLE I. A Partial List of Foreign-Chartered Medical Schools With Offices in the United States, 1984

Country Where Chartered	Medical School	US Address
Antigua	University of Health Sciences Antigua	Atlanta, GA
Dominica	Ross University (Formerly University of Dominica)	New York, NY
Dominican Republic	CIFAS University	Los Nietos, CA
Dominican Republic	Universidad de Nordestana	Brooklyn, NY
Dominican Republic	Universidad Technologica de Santo Domingo (UTESA)	Whittier, CA
Dominican Republic	World University	Washington, DC
Grenada	St. George's University	Bay Shore, NY
Mexico	Universidad Autonoma de Guadalajara	San Antonio, TX
Mexico	Universidad del La Salle	New York, NY
Mexico	Universidad del Noreste	New York, NY
Mexico	Universidad Valle del Bravo	McAllen, TX
Montserrat	American University of the Caribbean	Miami, FL
St. Lucia	Spartan Health Sciences University	El Paso, TX

of preceptorships under the "supervision" of individual physicians or of outpatient clinic experiences, accepted in lieu of inpatient hospital rotations. The duration, sequence, content, supervision and quality of such experiences are usually beyond the control of many of the medical schools.

Some schools have little desire to control and supervise the quality of clinical rotations taken by their students in the US. These schools often do not verify that clinical rotations were even performed. This lack of desire to supervise and control clinical rotations in the US stems from their need to place large numbers of students of uneven academic quality in clinical rotations. These schools place students wherever they can without regard for the quality of the experience. Some also literally accept, without verification, clinical rotations that students arrange for themselves. A small number of offshore schools such as those in Mexico possess clinical facilities for third and fourth year clinical rotations. American nationals, however, generally prefer to complete this segment of their studies in the United States. The offshore schools have been less than diligent in arranging clinical rotations in the US for American nationals. To do so requires the assumption of significant administrative responsibilities in the US and added costs for the schools. The placement of a student body of heterogeneous quality would still prove to be an onerous if not impossible task. Poorer quality students would go unplaced, with failure for this falling on the shoulders of the school. As it is now, many schools put the responsibility for placement in US clerkships in the laps of the students.

Another well-known characteristic of the offshore schools is their active newspaper advertising for enrollees. Such ads are often enhanced by the inclusion of Educational Commission for Foreign Medical Graduates (ECFMG) pass rate data for the school's students. What is not said is what percentage of ECFMG eligible students actually take the examination; the weaker students often do not sit for the examination. The 1983 experience with the ECFMG examination, in which the test had to be invalidated due to a security break prior to the examination, resulted in answers being sold far and wide at high prices. This raises the question of whether previous breaks have occurred.

Another serious concern is the sale of diplomas from two Caribbean schools in the Dominican Republic.[2] In January 1983 a naturalized Peruvian, Pedro de Mesones, was found guilty in Federal Court in Washington, DC for having sold 97 diplomas and for having taken money from 165 US residents seeking medical degrees. Ninety-six of them purchased diplomas that were issued by CETEC University (Universidad Centro de Estudios Tecnologicos) and CIFAS University (Universidad Centro de Investigacion y Formacion Assistencia Social), both of which are in Santo Domingo.

Des Mesones solicited students for CETEC and CIFAS by mail and arranged for diplomas to be awarded without their ever attending school. At least 13 of those who purchased diplomas received medical licenses in the US, and 36 were in hospital residency programs. A number of those who bought diplomas were pharmacists and podiatrists, individuals with some medical background. This experience points out the limitations of the ECFMG and other examinations. It tells us that formal attendance at medical school is not necessary for successful passage of the ECFMG.

ORIGINS OF THE OFFSHORE MEDICAL SCHOOLS

A significant number of American nationals have studied medicine abroad during the past few decades. Most were individuals who had been unsuccessful in obtaining admission to an American medical school. But many entered European university medical schools that had relatively high academic standards and completed their full course of study before returning to the United States.

Beginning in the late 1960s, the number of applicants to American medical schools began increasing disproportionately to the number of entering class positions. This increase was accounted for by the arrival of the large post-World War II "baby boom" cohort of the population at the graduate school level of education, and increased interest in medicine as a career.

By the early 1970s a number of European medical schools that had heretofore enrolled Americans and other foreign nationals began to raise barriers to entry. In part this was in response to pressures generated within these countries by increasing numbers of their own applicants. Diminished opportunities for medical school placement in Europe and ever increasing numbers of Americans desiring a medical education abroad created a favorable environment for the development of new schools in this hemisphere on various Caribbean islands and the enlarging of facilities in extant medical schools in Mexico to accommodate Americans.

At the same time the needs of Americans desiring a medical education in the United States were met in part by a rapid expansion in the number of American medical schools and the enlargement of class size in existing schools. This expansion was in response to federal and state inducements such as capitation grants, special project grants and mandates from state legislatures. It was said that these initiatives were undertaken to correct the physician shortage, which was claimed to exist in the 1960s. It should be remembered that some of these initiatives were undertaken, especially those at the state level, by legislators in response to the ever increasing demands of constituents for entry into medical schools.

Despite this enormous expansion of American medical schools, the demand continued to grow. In the early 1960s the annual number of medical school graduates in the United States averaged 7,000. By 1971, that number had grown to 12,000 and by 1983 to 17,000.[3] The increased demand in the early 1970s resulted in acceptance rates of 35.3% in the 1973–1974 application year (first year class 1974–1975).[4] By the 1980–1981 application year the percentage of accepted applicants rose to 47.0%. This change was accounted for by an increase in the number of first-year positions between the two periods from 15,000 to 17,286 and a decline in the total number of applicants from 42,624 to 36,727 (Table II). Thus it is far easier for an applicant to gain admission to an American medical school in 1984 than it was in 1974.

It follows from this that some of the academically better students who enrolled in the offshore medical schools in the mid-1970s would probably have gained admission to American medical schools had they been applicants in the early 1980s. It also follows that because of the decreasing number of applicants seeking an expanded number of places, fewer of the very best students will need to enroll in the offshore schools.

The establishment of some offshore medical schools was in a sense facilitated by changes in the curricula of American medical schools. The early 1970s witnessed the discontinuation of mandatory all-day laboratory sessions in biochemistry, physiology and pharmacology in a large number of schools. The philosophical basis of this policy is often said to be the lack of relevance of such laboratory experiences to the practice of modern medicine. Cogent opposition has been voiced against this argument by a number of medical educators. In part the disappearance or abridgement of laboratories in the basic sciences was also the result of student demands that came to the forefront as the undergraduate protest movement of the late 1960s moved into the medical schools. The invasion of clinical subjects, as either electives or as required courses, into the first two years of medical school also resulted in competition for limited time, a competition that laboratory exercises usually lost. Budget constraints on equipment and personnel were also factors. Greatly expanded class size in a number of US medical schools without the addition of new faculty made basic science departments less than enthusiastic about preserving laboratory exercises.

Laboratories for basic science teaching are costly to construct, and well-designed laboratory teaching exercises are expensive to run. In a sense the establishment of offshore medical schools was rendered more feasible financially because there was no need to build, maintain and operate the type of teaching laboratories once used in American medical schools. It was possible to set up a medical school by simply constructing lecture halls, classrooms and rudimentary laboratories, and bringing in visiting faculty. Caribbean islands in need of foreign exchange for sagging economies were only too willing to cooperate in such ventures.

TABLE II. Applicants to US Medical Schools, 1971–1972 Through 1981–1982*

First Year Class	No. Applicants	No. Accepted	Percent of Total Applicants Accepted
1971–72	29,172	12,335	42.3
1972–73	36,135	13,757	38.1
1973–74	40,506	14,335	35.4
1974–75	42,624	15,066	35.3
1975–76	42,303	15,365	36.3
1976–77	40,569	15,977	37.8
1977–78	36,636	16,527	45.1
1979–80	36,141	16,886	46.7
1980–81	36,100	17,146	47.5
1981–82	36,727	17,286	47.1

* Adapted from data provided by the Association of American Medical Colleges and the American Medical Association.

THE PROBLEMS OF RETURN

The opening of new offshore medical schools and the expansion of already existing schools in Mexico and elsewhere to accommodate the surge of American applicants did not in themselves create immediate problems in the US. What did create problems that required public policy formulation was the return of these US foreign medical students (USFMS) a few years later.

Unlike their predecessors, who largely attended European university medical schools, many of these more recent USFMS began to return not after gaining an MD or equivalent degree, but after two years of medical school. The absence of clinical teaching facilities at many of the offshore schools made it a necessity for students to return to the US for their clinical rotations. This coupled to reliance on individual student ingenuity in arranging rotations led to an untenable situation in New York State, in which hospitals of every kind were besieged with student requests for clinical training. Competing with their fellow students and with those from other schools and left to design their own curricula, undirected and unsupervised by the parent school, these students created serious concern among many medical educators and physicians. In addition many students were themselves dissatisfied with the anarchic state of their clinical medical education.

But there were also legal prohibitions to USFMS engaging in clinical rotations in New York State. The New York State Education Law stipulates that medical students can only practice medicine in the state if they are doing a clinical clerkship while enrolled in a medical school that meets standards established by the New York State Department of Education.[5] In 1960 the department approved all medical schools listed in the *World Directory of Medical Schools* published by the World Health Organization. This edition obviously did not contain the names of the newer offshore medical schools. However, advocates of the USFMS argued, with some justification, that this standard was rather arbitrary. Nonetheless Section 6526-8 of the law stood and violations were and are a Class E felony.

The issue was catapulted to the forefront of attention because of the large numbers of USFMS abroad and in clinical clerkships within New York State. The precise number of USFMS abroad is unknown for several reasons, despite attempts since the mid-1970s to ascertain the actual figure. Learned concensus places the current number at about 15,000. It also estimates that approximately 40% of these students are residents of New York State.[6] Most of these students prefer to return to their home state for their clinical rotations. This 40% figure is derived from annual applications of USFMS for direct transfer to US medical schools after the second year. This data is flawed, however, because there is no way of knowing what proportion of eligible candidates for direct transfer to advanced placement actually apply. It is supported, as Stimmel[7] points out, by data regarding the Fifth Pathway which in 1981 showed New York State to be training 535 (36%) of the national pool of 1,481 individuals. Jonas[8] sustains these data in noting that of the 3,000 counties in the US, Queens County in New York State has the highest ratio of USFMS to county population.

The New York State Department of Health's Office of Health Systems Management, which oversees hospitals in the state, became increasingly concerned over the presence of large numbers of USFMS in hospitals. In 1980, the office issued a memorandum[9] to all hospitals in the state, warning them that the presence of these students was illegal and that the institutions themselves could be found guilty of "aiding in the unlawful practice of medicine." Although the office originally intended to define which foreign medical schools met the Department of Education's standards, it eventually deferred this decision to the Division for the Professions of the New York State Board of Regents.[7] A series of events ensued that led to the promulgation and subsequent amending of regulations by the Board of Regents.[10] These regulations made it possible for students to re-enter New York State for the purpose of performing clinical rotations after completing their basic science training at an offshore school. Jonas[11] covers the historical development of these regulations in great detail and Monahan[12] details how the regulations function.

The current policy of the Regents was and is controversial. But it should be remembered that options proposed by opponents of this policy would be equally controversial had they been enacted.

The Path of Return for Clinical Clerkships

While admission to offshore medical schools has proven relatively simple for most applicants, returning into the mainstream of American medicine is no easy matter. The process of returning is becoming more difficult as screening examinations such as the ECFMG are brought up to par with the National Board of Medical Examiners (NBME) examination taken by most US medical school graduates for obtaining licensure.

For the USFMS the problems of returning begin earlier than the last year of medical school because of the unavailability or unsuitability of clinical clerkship rotations at the offshore schools.

The March 1981 regulations of the New York State Board of Regents, as described in detail by Jonas,[8] establish quality standards for clinical clerkships for USFMS in New York State. USFMS can only return to New York State to do clinical clerkships at hospitals with residency programs approved by the Accreditation Council on Graduate Medical Education (ACGME). The first two years of education at the offshore medical school must be approved by the New York State Education Department. The purpose of the approval is to guarantee that the first two years provide training that is adequate for doing clerkships in New York State.

In order to qualify for clinical clerkships in the state, students must take the Medical Sciences Knowledge Profile (MSKP) examination and achieve a score acceptable to the Department of Education.[10] This examination was originally developed by the NBME for the MSKP program of the Association of American Medical Colleges. Its purpose was and is to provide American medical schools with a means of assessing the knowledge of students who are being considered for direct transfer to their schools from an overseas school. The MSKP examination is given over a two-day period and covers anatomy, behavioral sciences, biochemistry, an introduction to clinical diagnosis, microbiology, pathology, pharmacology and physiology.[13]

The Path for Direct Transfer

In 1982–1983, 354 students from foreign medical schools transferred to American medical schools. About 98% were US citizens.[13] A total of 1,826 students from foreign medical schools applied for direct transfer and, of this number, 1,337 (73%) were students from seven proprietary medical schools in Mexico and the Caribbean.[14] As noted above, these students must all take the MSKP examination and achieve a score acceptable to the American medical school to which they are applying for advanced standing. Given the large number of potential USFMS available for direct transfer, the number who actually succeed in doing so is small.

The Fifth Pathway

In 1971 the Fifth Pathway program was established. It came into being because of constituent pressure to deal with USFMS who were returning from Mexican medical schools. These schools follow the general curriculum of the Universidad Nacional Autonoma de Mexico (UNAM). The course of study leading to the "titilo" (equivalent to an MD degree) is six years in duration, the last two years consisting of social service. The Fifth Pathway provides a route for USFMS in Mexican schools to re-enter the US medical system while by-passing the years of social service required for the "titilo."

After completing four years at a Mexican medical school, USFMS are eligible for Fifth Pathway positions. The Fifth Pathway provides a year of clinical rotations under the supervision of American medical schools. After completing this year, these USFMS are eligible for residency programs in the US, even though they do not have an MD or equivalent degree. Competition for Fifth Pathway positions was once keen, but in the last year there has been a sizeable drop in applicants (Table III).

The disparity between acceptances and enrollments in the program is explained by the fact that a number of ac-

TABLE III. Profile of Fifth Pathway Programs, 1979–1980 Through 1982–1983*

Academic Year	No. Applicants	No. Students Accepted	Percent Applicants Accepted	No. Students Admitted	No. Students Completing Program
1979–1980	2,459	666	27.0	547	516
1980–1981	2,709	630	23.2	491	474
1981–1982	2,444	491	20.1	510	506
1982–1983	1,676	474	40.6	388	392

* Derived from data provided in the "83rd Annual Report on Medical Education in the US 1982–1983" *JAMA*, 1983; 250:12.

cepted students decide to transfer to a Caribbean medical school before enrollment in the Fifth Pathway. Fifth Pathway programs assess applicants on the basis of a screening examination, often that of the ECFMG. Students are also interviewed and their Medical College Admission Test (MCAT) scores and undergraduate grade point averages (GPA) are assessed. Approximately 20% of all American medical schools have Fifth Pathway programs.[13] The overall program has been controversial and it is likely that it will be discontinued. Tuition costs in programs operated by the State University of New York have risen sharply in the past two years creating a strong disincentive for student participation.

However, the more important reasons for the probable demise of the Fifth Pathway are a recent decline in the annual number of applicants (Table III), the tendency of USFMS to enroll in Caribbean medical schools that grant an MD degree after four years of study rather than attend Mexican schools where even after four years and a Fifth Pathway year one does not have an MD degree, and the increasing tendency of many USFMS in Mexican medical schools to transfer out to Caribbean schools after two years in Mexico.

The competition from the Caribbean schools is already being felt by the Mexican medical schools. Over the past few years there has been a gradual and steady decline in the number of US national applicants to the Universidad Autonoma de Guadalajara and to the Universidad del Noreste.[15]

To counter this, these two universities have instituted curricular substitutions for the required years of social service in Mexico. Guadalajara has arranged for an internship in a Spanish-speaking area of the US to discharge part of the social service responsibility, along with a required third year in Mexico (heretofore Guadalajara students could go to the US after two years). The Universidad del Noreste is following this same route but is attempting to grant the "titilo" after four years of training, three of which would be in Mexico. It has obtained the approval of the state of Tamaulipas, where it is located, for doing this. But if, as seems likely, a third required year in Mexico plus an internship can be substituted, then there would be little interest in the Fifth Pathway Program and it would be discontinued.

These efforts, however, may not be sufficient to stem the shift of applicants to the Caribbean schools. They offer an MD degree after four years. The Mexican universities offer a "titilo," and in New York State a recipient of this title may not use the letters MD after his name. If the Mexican universities are successful in obtaining permission to grant the "titilo" after four years or after the internship, they still will be non-competitive with the Caribbean schools. The new plan would require students to do their third-year clinical clerkships in Mexico. Most USFMS prefer to do this year in the US—another advantage of the Caribbean schools. Even if the "titilo" is received after four years, a USFMS graduate of a Mexican school would have to do three years of post-graduate training, obtain a license to practice medicine and then after three years of practice apply to the University of the State of New York for an MD degree. This degree would be conferred by the University of the State of New York and not by the Mexican University.

Those USFMS who now go the route of the Fifth Pathway can obtain a license to practice in New York State much sooner—after the fifth pathway year. They too can apply for an MD degree from the University of the State of New York, but much sooner, after three years of residency training.[16]

TRANSFERS BETWEEN SCHOOLS

USFMS in Mexico frequently transfer to Caribbean schools after two years. Seldom do students transfer from Caribbean to Mexican schools. Transfers usually do not require the student's physical presence at the Caribbean home campus in question and are handled in the US offices of these schools. These transfer students then engage in clinical clerkships in the US and never set foot on the Caribbean island in question. There are also frequent transfers between Caribbean schools.

For obvious reasons, financial loss included, the Mexican schools discourage transfer. They can do this by establishing barriers for obtaining a certified transcript of performance during the first two years. USFMS at these schools have gotten around this by using class grade records (bolletto), which are unofficial documents, often acceptable to a number of Caribbean schools. Thus large numbers of USFMS "disappear" from the Mexican schools at the end of the second year and sometimes sooner. Officials of the Mexican schools assume that most of these students transfer to Caribbean schools.[17]

It is difficult to quantify the magnitude of these transfers because of the significant numbers of students who quit school altogether without informing the university. Poor follow-up and tracking on the part of the Mexican schools compounds the problem.

THE CURRENT SITUATION

Although controversial, the current regulations of the New York State Board of Regents provide quality standards for governing the clinical clerkships of USFMS in New York State. These regulations restrict the entry of USFMS into clerkship positions in the state through the use of the MSKP examination, site visit based approval of the first two basic science years as adequate for the performance of in-state clerkship, and clear definition of hospitals where clerkships may be performed (those with ACGME approved residencies). Preliminary evidence demonstrates that these measures have been successful in providing entry and opportunity to the best qualified students while preventing the entry of unqualified USFMS. Only 30% of the students who took the MSKP examination from one Mexican medical school in 1983 passed. In the pre-regulation period, many of these examinees would have attempted to return to New York State for clerkships. Unsuccessful USFMS examinees are now flocking to adjacent states, most of which do not have regulations governing clinical clerkships for these students. As the number of USFMS barred from New York State increases, these other states will be forced to deal with the problem as well.

In 1981 opponents of the Regents' regulations predicted that the "satisfactory" score for the MSKP examination would be set so that the majority of examinees could enter clinical training.[7] So far this has not occurred. In fact, based on available information, most USFMS are now unsuccessful in obtaining clinical clerkships in New York State.

Given the nature of most offshore schools, and their enrollment of large numbers of students who have neither the intellectual ability nor the skills to be adequately trained physicians, it is tempting to advocate a course of absolute prohibition from returning. This would deny opportunity to that proportion of USFMS who do have the abilities and skills to be competent physicians. In granting USFMS the opportunity to do clinical clerkships in New York State, the Regents has in no way guaranteed eventual licensure. All of these students still face the hurdles of the ECFMG examination (to be replaced by July 1985 with the new Foreign Medical Graduate Examination in Medical Sciences (FMGEMS)). This latter examination will also replace the Visa Qualifying Examination (VQE). Students must also pass the examination of the Federation of State Medical Boards (FLEX) to obtain licensure.

Those who would prohibit entry of USFMS into this state for clinical clerkships can and do muster a number of convincing arguments. The most recent of these, and indeed the one that will have a major impact on medical care finances in this country, is the growing physician surplus in the US. It is estimated that under the present means of testing and screening, 50% of this surplus will consist of United States and alien foreign medical graduates.[18] Thus there is no convincing argument that we need these foreign medical graduates (FMG).

A national policy and national measures have proven elusive because licensure for the practice of medicine is the right of individual states. It is unlikely that individual states with large numbers of USFMS citizens could politically and pragmatically legislate their exclusion. The Regents, who in this state are appointed by the legislature, were and are not likely to issue regulations centered on absolute exclusion. And those who hope otherwise are out of touch with the political process that characterizes American democracy. There are deficiencies in the current program of the Regents, and the Regents have made consistent efforts to improve the regulations since they were first promulgated.[19]

PRESENT AND FUTURE PROBLEMS

There are several separate but related problems concerning the FMG, both US and alien, that will overshadow those of USFMS in clinical clerkships. These include the physician surplus, which is already here and which will continue to mount. If present trends continue there will be 250 physicians per 100,000 population in the US, compared to 168 in 1970. Presuming no changes in medical care financing, this surplus will cause an enormous drain on the nation's gross national product. It is more likely, however, that the surplus will speed cost containment measures, some of which may be draconian, cause unpleasant levels of competition manifest in many ways, and encourage the development of practice models not feasible with fewer physician members.

Those who find comfort in believing that the surplus can be handled through diffusion to underserved rural and inner city areas are mistaken. The diffusion has already taken place.[20,21]

Both USFMGs and alien FMGs will increasingly encounter difficulties in finding residency positions. This has already begun. The results of the National Resident Matching Program (NRMP) for 1983 show that only 26% of the 3,618 alien FMGs matched.[22] Only 49% of USFMGs matched in 1983. In the 1984 matching program only 22% of 4,212 alien FMGs matched and 44% of USFMGs.[22] These data and other trends analyzed by Stimmel and Graettinger[18] and others tell us that the proportion of unmatched USFMGs and alien FMGs will only increase as the output of American medical schools remains high and the number of residency positions stationary.[18] In the 1983 NRMP the percentage of alien FMGs increased by 312% and that of USFMGs by 270% over 1980.[18] In the former case the increase is in part accounted for by unsuccessful candidates from previous years re-applying. In the latter, one is witnessing the inevitable flow of the pipeline from the offshore schools.

These trends will continue and will result in large numbers of USFMGs and alien FMGs in this country who cannot obtain residency positions. Their only alternative is to pursue general practices in one of several states that do not require residency training for licensure.[18] However, increasing numbers of unsuccessful residency program candidates will eventually form a political constituency capable of inducing legislative and judicial remedies to their problems. One of these remedies could be the establishment of preceptorships outside of hospitals in lieu of residency training. Most agree that this would be a very undesirable course of action for American medicine.

There has been widespread dissatisfaction with the VQE

TABLE IV. Characteristics of Examinations for US and Foreign Medical Graduates, 1984

Exam	No. Days	No. Questions Basic Sciences	Clinical	Total
NBME I	2	1,000	—	—
NBME II	2	—	900	—
NBME III	1	—	760	2,660
ECFMG	1	114	306	420
VQE	2	500	450	950
FMGEMS	2	500	400	900
FLEX	3	540	1,300	1,840

(administered to alien FMGs) and the ECFMG examination (Table IV).Critics have pointed out, with justification, that neither of these examinations adequately assesses medical knowledge as do Parts I, II and III of the NBME given to most US medical students. The ECFMG has a total of only 114 questions in the basic science, compared to 1,000 on Part I of the NBME test. Even the FLEX examination that FMGs eventually take if they have passed all the other hurdles has about half the number of basic science questions of Part I of National Boards. There are 1,300 clinical questions in FLEX, versus 1,660 questions on Parts II and III of the National Boards.

There was a time when the US was in need of FMG manpower. This is no longer the case. And the ECFMG, some have argued, was structured to ease the entry of that much needed manpower into the US. Standards were raised in 1976 with the institution of the VQE exam for alien FMGs. This is a much more difficult test with a pass rate for all FMGs of about 27% compare to 40% for the ECFMG.[18] The VQE is more difficult because it contains almost five times the number of basic science questions as the ECFMG examination.

In order to deal with this problem the ECFMG is instituting in 1984 the new Foreign Medical Graduate Examination in the Medical Sciences (FMGEMS). By 1985 it will replace the ECFMG and the VQE. This two-day examination will contain 500 basic science items on day one and 450 clinical items on day two. This 950 total is far more than the total of 420 on the ECFMG and equals the 950 on the current VQE. It will be eqivalent to Parts I and II of the National Boards, but will contain 1,000 fewer questions than those two examinations combined.

It is likely that the pass rate for all FMGs will fall to levels seen with the VQE examination. This will result in the build-up of very large numbers of both alien FMGs and USFMGs who cannot qualify for residency positions or for eventual licensure in most states. And among those who do qualify, the chances of finding placement will be extremely limited.

This phenomenon has already begun. Significant numbers of both alien and USFMGs, some with ECFMG certificates, are presently taking undergraduate "electives" in some teaching medical centers, because they have not been able to obtain residency positions. It is a violation of the New York State Education law for individuals with an MD degree to take undergraduate clinical rotations. And clearly there is the danger that FMGs may, in the future, attempt to pass off such rotations as residency training or seek legislative action to recognize such experiences as adequate substitutes for residency training. The increasing difficulties that FMGs will encounter in finding residencies may lead to a range of actions on their part to get back into the mainstream of American medicine. Some have begun advertising their availability in newspapers and medical journals. Others are willing to do residencies without a stipend, and some are even willing not only to forego a stipend but also to pay tuition to a hospital that will take them on as residents.

It seems certain that the interplay of a number of variables will lead to large pools of unsuccessful MSKP, FMGEMS and FLEX candidates as well as unsuccessful residency program candidates among USFMGs. These individuals may present significant professional and political problems in New York State and other states as well. They and their advocates may seek judicial or legislative remedy, or both for their problems; their success is difficult to predict. Expansion of residency program positions seems unlikely to occur, because it runs counter to medical manpower needs and cost containment and is under the control of diverse national bodies not susceptible to intrastate lobbying groups. But sufficient lobbying could be launched to expand the number of residency positions in the state.

Finally, the prospects of either legislative or judicial relief for the problems of USFMGs have been lessened by the disclosure of widespread diploma sales from two offshore medical schools in the Dominican Republic.[23,24] It is estimated that 2,000 fraudulent diplomas were issued by two medical schools in the Dominican Republic.[25] These two schools, CETEC and CIFAS were closed by the government of the Dominican Republic on May 11, 1984.[26] Fifteen administrators from the two schools were arrested, and warrants were issued for the arrest of many others.[27] Because of events in the Dominican Republic, many legislators and other supporters previously sympathetic to the needs of USFMGs may now prefer to distance themselves from the situation.

Alternatively, unmatched USFMGs could launch an effort to have New York State waive residency program training as a condition for licensure. This would create a subclass of physicians in this state who are not needed and who would jeopardize the quality of medical care. This is not likely to happen, however, because diploma sales have cast a shadow of suspicion over the credentials of all USFMGs from offshore medical schools. Many in government will be reticent about acting on their behalf. Because of this suspicion, it is almost a certainty that USFMGs from offshore medical schools will encounter increasing difficulties in gaining residency positions. Hospitals, wary of the stated credentials of USFMGs, will adopt policies that will accelerate the growth of the unmatched pool of USFMGs in the United States. Whether this will lead to declining enrollments in the offshore schools in the long term is an open question.

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IS THE ESTABLISHMENT DEFENSIBLE?

McNerney was correct when he pointed out that the alleged doctor shortage of the 1960s was a figment of somebody's imagination. Rightly or wrongly, medical schools geared up to meet the physician shortage, aided and abetted by capitation grants, special project grants, and mandates from state legislatures. It was politically popular to institute new medical schools and to expand those already in existence. This public policy doubled the number of graduates of our medical schools in a little over 10 years. For most of the 1970s a debate took place over whether or not there was a physician surplus, but there is no longer any doubt about it. In 1970, the physician-to-population ratio was 168 to 100,000 population; it is now in excess of 190 per 100,000 and in California it is 220 per 10,000. In 1990 it will be 250 per 100,000. Only Israel and the Soviet Union have more physicians. And although there are now some moves toward contraction, it has been difficult. It is always easier to expand than to contract—particularly in medicine, a profession that seems to have lost its ability to control its own growth . . .

To sum up the manpower picture, we have too many doctors, particularly specialists, and we need to institute birth control. We need to quit training our own competition, because it is eating us alive and weakening the very training programs of which we are so proud.

—RG PETERSDORF
N Engl J Med 1983; 309:1053–1057

The historical and theoretical basis for the New York State Board of Regents' policy concerning US foreign medical students

STEVEN JONAS, MD

The issue of United States foreign medical students (USFMS) and graduates (USFMGs) is becoming increasingly complex, as indicated by the recently published physician supply study of the Board of Regents of the New York State Education Department[1] and the inaugural address of the new president of the Mount Sinai Medical Center, James Glenn, MD.[2]

The list of policy issues related to the matter of United States foreign medical students and graduates is lengthy. It includes, but is not limited to, the following: physician supply, utilization, and distribution; primary care and specialization in medicine; non-physician primary care practitioners; physician work patterns, income, and mode of payment; and the content and process of medical education.[3,4]

POLICY OF THE BOARD OF REGENTS OF NEW YORK STATE

The current policy has a narrow focus, addressing USFMS in clerkships in New York State hospitals and outlining licensure requirements that govern all foreign medical graduates. It does not speak to issues concerning the supply of physicians. The policy was created in response to proprietary medical schools in the Caribbean and Mexico that were established specifically for United States citizens. While the Autonomous University of Guadalajara, the original "US foreign medical school," does have clinical facilities, most of the Caribbean and some of the newer Mexican schools have little or nothing in the way of clinical teaching resources. Thus, they must send their students elsewhere for clinical training, becoming in essence two-year medical schools. Many of these schools made arrangements with hospitals in New York State to provide clinical clerkships, but many of these hospitals did not otherwise have a teaching program. This situation created ethical and legal problems for both the Department of Education and the Department of Health.

In the spring of 1981, the Board of Regents adopted a set of regulations to deal with these problems.[5,6] The regulations do not accredit foreign medical schools, but provide approval for the purpose of placing students in clinical clerkships in hospitals in New York State. The regulations also set special requirements for all foreign medical graduates who wish to be licensed in the state. There are four licensure requirements: (1) if the candidate has done his or her undergraduate clerkships at a New York State hospital, the school must have been approved for New York State hospital clerkship preparation; (2) the student must have obtained a score on the Medical Sciences Knowledge Profile examination or its equivalent that is "satisfactory to the Department of Education" before taking the clerkships; (3) the candidate must have completed three years of approved residency training; and (4) the candidate must pass the Federation of State Medical Boards Examination (FLEX). The three-year residency requirement was considered to be especially important for quality control. Although studies demonstrate clear differences in test performance between US and foreign medical graduates, it is not possible to discern differences in clinical performance between US and foreign medical graduates who have taken US residency training.[6]

PROPOSED SOLUTIONS

One approach to solving the USFMS problem is to focus on the supply side, for both US and foreign graduates. Donald Louria, MD recently summarized this approach:[7] "(1) Medical school enrollment must be cut by 20% . . . . (2) Measures must be taken to prevent a massive influx from medical schools outside the United States . . . . (3) We must reverse the short-sighted attempts to prevent non-immigrant foreign-trained physicians from taking postgraduate training in the United States . . . ."

The third provision would benefit both the countries of origin and those hospitals whose residency programs are now barely filling with US citizens after many years without them. These hospitals would be looking for applicants due to the first two provisions of Louria's plan. Louria's position is identical to those of many agencies such as the Graduate Medical Education National Advisory Committee (GMENAC) and the American Association of Medical Colleges (AAMC). It proposes direct solutions to identified problems based on a rational planning approach.

Unfortunately, in this instance such an approach may not work. First, even the proposed surplus of physicians[8] does not make medical schools take kindly to the threat of closure.[9] Second, not everyone is convinced that there is or will be a surplus. A recent editorial in *American Medical News* presents an open mind on the question.[10] It was firm on one point, however. If there is a surplus, the way to deal with it is through market forces, not centralized planning.

Solon J. Stone, a member of the Advisory Committee to the New York State Regents' Physician Supply Study,

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Address correspondence to Dr Jonas, Professor, Department of Community and Preventive Medicine, State University of New York at Stony Brook, Stony Brook, NY 11794-8036.

chose to present his views in a Supplemental Report:

> I have written it as a caveat against unqualified reliance upon those parts of the report which indicate a doctor surplus and because I think recent assumptions by the news media that there is or will soon be a doctor glut are rebutted by the facts.[1]

It is important to note that Stone's views reflect those of the Chancellor of the Board of Regents, Willard Genrich:

> The consumer of medical services would welcome a 'doctor surplus.' . . . As a matter of law, the economic policy of the United States is to promote competition among medical doctors . . . . There will not be any meaningful competition in the consumer sense among doctors until there are more than enough doctors to satisfy the demand for service . . . . The report's estimates of the need for medical services may be erroneous.[1]

In his comment on the last point, Stone stated his concern with geographic maldistribution, and his view that the unmet demand for medical school places reflects an unmet need for physicians. He also justifies his position by pointing out that there are more hospital residency positions than there are US graduates to fill them, indicating a shortage of US graduates. At the same time, he says that there is a shortage of residency slots to accommodate US foreign medical students. In conclusion Stone says, "The consumer does not believe there is or can be a doctor shortage."[1] Stone's position is a popular and powerful one.

Another point of view suggests that the lack of available house-staff positions to accommodate all US medical graduates and FMGs, which is likely to be a problem soon, will leave out a significant number of FMGs without the need for legislation.[11] Until recently I subscribed to this view. I am now convinced, however, that there will be a legislative response in the other direction. The Regents will be forced to reduce the three-year requirement, new residency slots will be forced upon the hospitals with some—but not enough—money to fund them, and there will be some half-hearted attempts to deal with geographic maldistribution. (The only way to solve that problem, certification-of-need for private doctors' offices, will not be attempted.) This all means that the "free market" will be given a further opportunity to act.

In this regard, it is interesting to consider the effects of the widespread practice of issuing fraudulent degrees operated by several institutions in the Dominican Republic.[12] The practice, apparently involving thousands of people, might result in the tainting of every Caribbean medical degree, past or future. It might thus accomplish what many powerful medical interests in the United States could not accomplish: the virtual shut-down of the off-shore proprietary medical school system. It might, on the other hand, lead to demands for closer scrutiny of the off-shore schools, possibly involving accreditation. This is the position the schools' political supporters will probably take, and it would lead to more, rather than less, state involvement in the operation of the off-shore schools. Furthermore, if accreditation were to be instituted, there would probably be an increase, rather than a reduction, in output.

FUTURE PHYSICIAN SUPPLY

If there will be an ever-increasing flow of physicians into the medical marketplace, and if the American medical schools can do nothing to stop it other than reducing their own output, what could they do to make a positive contribution to the situation? To answer that question, one must first examine what medical practice may look like by the end of the century. This picture is based in part upon developments that are taking place in certain parts of the country.

There will be many physicians. Even an approximate number is unavailable, because the offshore output is impossible to predict. The quality will probably be more uneven than it is today. There will be many more physicians working in salaried settings. As competition increases, the lure of private practice will dim. Physician income will level off and then decline. Those who have in the past said that physicians can infinitely increase the demand for their own services will be proven wrong. So too will those who have said that the public will use an infinite amount of medical service if it is without charge at time of use. A finite limit on product use will be reached relative to population size.

New physicians interested in establishing a private practice in areas with a large physician population will find that their only choices are buying a practice or entering a partnership, probably after working on salary for some years. Private practices will be readily available in areas that lack sufficient medical personnel. However, since there will probably still be no national health insurance, that sort of private practice will not be accompanied by the prospect of a high income.

Physicians will be looking for new products to market. Preventive medicine will gain in importance. Doctors may begin to offer evening and weekend hours and house calls. They may begin to spend more time communicating with their patients and educating them. (As a by-product, malpractice litigation will probably decline.) They may look for new practice forms, working in cooperative relationships with nurse practitioners, physicians' assistants, and even chiropractors in primary care. Doctors will also have to pay attention to and know a great deal about aging.

EDUCATING AND TRAINING FUTURE PHYSICIANS

If these things do happen, the doctors of the future will need different and additional knowledge, skills and attitudes than they have now. This will provide United States medical schools with the opportunity to distinguish themselves from their foreign competitors. Doctors of the future, if they are to survive in the medical marketplace, will need communication and educational skills. They will need a high level of knowledge of health promotion and disease prevention. They will need health planning, epidemiologic, practice management, and marketing skills. The ability to work effectively with non-physician health professionals and to use community resources will become increasingly important. They will have to know how to provide informed consent to an increasingly demanding public, and how to incorporate technological advances into their practices. Finally, they will have to know how to use a computer for quality assurance, continuing professional and patient education, and as an aid to medical practice.

Most medical curricula are ill-equipped to produce this kind of practitioner. In fact, those students entering school now will be entering practice in the mid-1990s. Many of them will lack the skills necessary to compete with established practitioners, organized practice settings, and the other health professions. If the schools are to serve their future graduates well, they should begin changing now.

The AAMC's General Professional Education report will address some of these problems, probably emphasizing a self-directed, student-centered learning approach, stressing the need for clinical relevance, and proposing the use of explicit learning objectives.[3] Furthermore, irrelevant basic science teaching, which inundates medical students in the first two years, should be removed. Thus, clinically relevant basic science knowledge, now submerged in a morass of distractions, could be learned more efficiently. Aided by the "high-impact disease" focus of the new FLEX examination, undergraduate clinical teaching could be geared more toward the practice of medicine in the community rather than in the tertiary-care teaching hospital. More importantly, the learning environment could be changed to help the student improve his or her interactive abilities rather than overwhelming the student with soon forgotten knowledge. Information could be presented in a manner that enhances rather than diminishes retention. As in medical practice itself, basic science could be integrated with clinical medicine in the learning experience.

The American medical education system must begin to prepare for the future. Because it is unlikely that any meaningful controls will be placed on the production of physicians, the medical marketplace in 2000, less than 16 years from now, will differ greatly from its present form. Physicians will need different skills, knowledge and attitudes if they are to compete effectively. Medical schools must rise to the challenge of preparing physicians for the 21st century.

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New York State's approach to clinical clerkships for students in unaccredited medical schools

THOMAS J. MONAHAN

New York State's Education Law establishes several categories of individuals who may practice medicine in this state without a license. One of these groups is composed of students who are enrolled in medical schools that meet standards acceptable to the New York State Education Department and who are performing clinical clerkships in New York State hospitals.[1]

Until recently most students performing clinical clerkships in New York were enrolled in medical schools that were registered with the education department or accredited by the Liaison Committee on Medical Education. And for many years, foreign nationals who were enrolled in medical schools in their own country had participated on occasion in a short-term clinical experience in New York State hospitals. Clerkships performed by students who matriculated in schools outside of the United States and Canada were few in number, were restricted to major teaching institutions, and were limited to approximately 12 weeks or less during the last two years of medical school.

In the mid and late 1970s, however, a new and different type of clinical clerk began appearing in significant numbers in New York's health care facilities. These clinical clerks were usually United States nationals enrolled in unregistered and unaccredited medical schools located outside of the United States and Canada. By 1979 it was becoming apparent that many such clinical clerks were functioning in New York State hospitals. As a result of this phenomenon concern developed over the need to assure that such students were receiving an adequate medical education. It was also necessary to protect the health and welfare of the people of New York State who would be seeking medical care at the facilities in which these students were performing clinical clerkships. Based on these concerns specific requirements were developed by the Board of Regents under which students enrolled in unregistered and unaccredited medical schools might serve in clerkships in New York State hospitals.

HISTORY OF THE REGULATIONS

A position of barring students in unregistered and unaccredited medical schools from doing clerkships in New York was ruled out on legal and practical grounds. To adopt a policy of barring such students unequivocally could be considered arbitrary, since students from some unregistered and unaccredited schools had been admitted to clerkships under New York law and regulations for many years. A policy of allowing some schools to send clerks and denying the privilege to others could only be sustained on the basis of standards and procedures for selection. These issues were discussed by the Board of Regents of the University of the State of New York at several meetings, and regulations were developed concerning students seeking clinical training in New York State. In February 1981 public hearings were held concerning the proposed regulations, and on March 26, 1981 the Board of Regents amended the Regulations of the Commissioner of Education with regard to clinical clerkships undertaken in New York hospitals by students enrolled in unregistered and unaccredited medical schools. These regulations became effective May 1, 1981[2] and were further amended by the Board of Regents on December 17, 1982 and October 21, 1983.[3] The later amendments further define the regulations regarding clinical clerkship eligibility.

The Regents' policies on clerkships relate to clinical rotations that are intended to constitute the third or fourth years of medical education, served under the aegis of unregistered or unaccredited medical schools. These policies are not intended to apply to students enrolled in programs that are registered by the State Education Department or programs accredited by the Liaison Committee on Medical Education or the American Osteopathic Association—basically encompassing all United States and Canadian medical schools.

In general, the regulations restrict all clinical clerkships undertaken by students in unregistered and unaccredited medical schools to teaching hospitals and stipulate that no clinical clerkships are to be undertaken in non-teaching hospitals or other health related facilities or agencies. A teaching hospital is defined as having a residency program approved by the Accreditation Council on Graduate Medical Education or an equivalent accrediting agency acceptable to the State Education Department, or which is part of such a program through an affiliation approved by the Accreditation Council on Graduate Medical Education or an equivalent agency acceptable to the State Education Department. A clinical clerkship may be performed only in the area in which a teaching hospital has an accredited residency program. A clinical clerkship in medicine, for example, may be performed only in a teaching hospital that has an accredited residency training program in medicine.

SPECIFIC REQUIREMENTS FOR STUDENTS

The regulations on clinical clerkships establish different sets of requirements depending upon where a student is in the sequence of his or her medical education and the total number of weeks of clerkship that are to be completed. For participation in clinical clerkships, in New York State

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Address correspondence to Mr Monahan, Associate Executive Secretary, New York State Board for Medicine, The New York State Education Department, Albany, NY 12230.

teaching hospitals, that total more than 12 weeks within a two-year period, the regulations provide for four categories of students: (1) A student in an unregistered and unaccredited medical school who was engaged in a clerkship in New York State prior to May 1, 1981 is permitted to engage in additional clerkships without meeting any of the requirements specified in the regulations.

(2) A student who was enrolled on or before September 25, 1980 in the unregistered and unaccredited medical school in which he or she is matriculating, but who was not engaged in a New York State clerkship before May 1, 1981 is required to (a) achieve a score satisfactory to the State Education Department on the Medical Sciences Knowledge Profile (MSKP) examination, and (b) do the clerkship in a teaching hospital that has an approved residency training program in the field in which the clerkship is conducted.

(3) With the exception established in category 4 below, a student who entered the unregistered and unaccredited medical school in which he or she is matriculating after September 25, 1980 is eligible to participate in clerkships only if, in addition to meeting the requirements relating to MSKP, the foreign medical school in which the student is enrolled has been reviewed and approved by the State Education Department for placing its students in clinical clerkships in New York. In addition, the clerkships may be performed only in the teaching hospitals with which the foreign medical school has formal agreements approved by the State Education Department.

(4) A student who entered the unregistered and unaccredited medical school in which he or she is matriculating after September 25, 1980 but before May 1, 1981 may participate in clinical clerkships, provided that such clerkships are conducted in teaching hospitals, that the student has received an acceptable score on the MSKP examination, and that the medical school has submitted an application for approval.

Students enrolled in unregistered and unaccredited medical schools that have not applied for approval or have not been approved are eligible to engage in clerkships of 12 weeks or less in teaching hospitals during two academic years. Such students are exempt from the requirement of a satisfactory score on the MSKP examination, but must present the teaching hospital with a letter of eligibility, issued by the State Education Department, to participate in clinical clerkships.

All students enrolled in unregistered and unaccredited medical schools who wish to perform clerkships in New York must present evidence of their status to the teaching hospital in which they seek to undertake clerkships as follows: (1) Students who were engaged in clinical clerkships in New York State prior to May 1, 1981 must present a letter issued by the State Education Department attesting to their exemption from the requirements.

(2) Students who were not engaged in clinical clerkships in New York State prior to May 1, 1981 but who were enrolled in the unregistered and unaccredited medical school in which they are matriculating on or before September 25, 1980 must present a certificate issued by the State Education Department to the teaching hospital in which the clerkship (or clerkships) is to be performed, indicating that the student received an acceptable score on the MSKP examination.

(3) Students who enrolled in the unregistered and unaccredited medical school in which they are matriculating after September 25, 1980 (with the exception noted in the following paragraph) must be enrolled in a school approved by the department and must present a certificate issued by the department indicating that the student received an acceptable score on the MSKP examination. Students enrolled in schools approved by the department are permitted to engage in clinical clerkships only in teaching hospitals that have affiliation agreements with schools in which such students are enrolled.

(4) Students who enrolled in the unregistered and unaccredited medical school in which they are matriculating after September 25, 1980 but before May 1, 1981—and if the school has submitted an application for approval—must present a certificate issued by the State Education Department to the teaching hospital in which the clerkship is to be performed indicating that the student received an acceptable score on the MSKP examination.

(5) Students enrolled after September 25, 1980 in unregistered and unaccredited medical schools not approved by the department or which have not submitted an application for approval may perform up to 12 weeks of clerkships in a teaching hospital during two academic years. The student must present the teaching hospital with a short-term clerkship letter of eligibility. The letter issued by the State Education Department will state the name of the student, the medical school in which he or she is enrolled, the teaching hospital in which the clerkship is authorized to be performed, the inclusive dates of the clerkship, and the specialty area of the clerkship.

The MSKP Examination

Two of the major components of the regulations governing clinical clerkships are the Medical Sciences Knowledge Profile (MSKP) examination and the system for reviewing the educational programs of medical schools located outside of the United States and Canada. The MSKP is an examination designed to evaluate an individual's knowledge of the seven basic science areas, as well as knowledge of basic clinical diagnosis. To be eligible to serve in clinical clerkships in New York State, students must achieve a score on MSKP that indicates a level of knowledge comparable to the minimum standard required of medical students in accredited United States schools to pass Part I of the licensing examination developed by the National Board of Medical Examiners (NBME). To pass, United States medical school students must achieve a score that is equal to or higher than 1.2 standard deviations below the mean reported by NBME.

The MSKP consists of eight subtests which are scored separately. For each subtest the candidate receives a score that ranges from a low of 1 to a maximum of 9. The eight subtest scores may then be added to obtain a total. The minimum possible total is 8 and the maximum total is 72. Because Part I of the NBME examination and MSKP use different score reporting systems and are based on different means, it is necessary to use a special reference group to establish a comparable level of performance on both tests. For each administration of MSKP, a reference group of second-year students in United States medical schools takes both MSKP and Part I of the NBME examination. Score distributions for Part I and the eight subtests of MSKP are established for this special reference group, and for each portion of MSKP the specific score that corresponds to 1.2 standard deviations below the mean of the reference group is determined. The eight subtest scores are then added and a total is established as the minimum performance necessary for clinical clerks in a specific year. Although the minimum satisfactory total score may vary from year to year, it always represents the same level of performance of students in unregistered and unaccredited schools relative to the reference group of United States medical school students. The minimum acceptable total scores to date have been 39 (1980), 41 (1981), 43 (1982), 44 (1983).

SITE VISIT GUIDELINES

An unregistered and unaccredited medical school may seek approval to place students in clinical clerkships in teaching hospitals in New York State by submitting an application to the State Education Department. The medical school must submit a completed Data Base Document along with current catalogs, handbooks and all other materials concerning the institution's program of medical education. The school must also agree to cover all expenses connected with the evaluation process, which currently costs about $30,000.

The department's system for the evaluation of medical school programs for the placement of clinical clerks in New York is based on generally accepted procedures for academic program review. The institution presents documents, in English and in a format specified by the department, that provide information required by the department and relevant to the Regulations of the Commissioner of Education and the Guidelines for Evaluation of Medical Programs.[4] The department then designates several persons to review these materials. After the initial review of the materials submitted by the school, a site visit team visits the campus and representative clinical facilities which may be located at other sites—New York hospitals, for example. The site visit team usually includes at least one staff representative of the department, a member of the State Board for Medicine, and three or four medical educators and practitioners who have experience in evaluating medical programs.

Prior to the visit, the school requesting approval must provide extensive information concerning the curriculum, faculty, students, resources, and administration of the institution. The site visit provides an opportunity to verify the accuracy and completeness of the data provided and permits an in-depth review of such program components as (1) the depth and breadth of the curriculum and the integration of the basic sciences and clinical experiences; (2) the use of acceptable standards of admission, the maintenance of student records and the provision of student services; (3) the adequacy of basic science facilities including faculty offices, laboratories, classrooms, libraries and other resources; (4) the levels of faculty and student morale, intellectual stimulation and academic achievement.

Program evaluators use specific guidelines to review the program of medical education. These guidelines include but may not be limited to the following: (1) The medical school is organized as a definable academic unit, responsible for an educational program of not less than 32 months which leads to the MD degree or equivalent degree as determined by the department. The institution is listed in one or more of the generally accepted resource volumes in international education, and its program is legally recognized and approved for the training of physicians by the competent authorities of the jurisdiction in which it is located. (2) A complete educational program is maintained, the structure and content of which provide an adequate foundation in the basic and clinical sciences. (3) An administrative and governing system is provided which allows the school to accomplish its objectives. (4) The faculty is composed of a sufficient number of representatives of the biological, behavioral, and clinical sciences to implement the objectives of the institution. (5) Acceptable standards concerning admission requirements and the student selection process are in place, and a system is maintained for keeping adequate student records. (6) Financial resources are available that allow the institution to conduct its program in a satisfactory manner. (7) Adequate facilities, or access to them, including buildings and equipment, are available to provide an environment conducive to the maximum productivity of faculty and students in fulfilling the objectives of the school.

After the site visit to the home campus of the medical school and the clinical affiliates in New York State, program evaluators are asked to submit reports on those areas for which they have been assigned responsibility. A composite report is then prepared and submitted to a departmental review committee for consideration. The review committee, composed of department staff and a member of the State Board for Medicine, reviews and discusses the site visit report. The final action is the responsibility of the Deputy Commissioner for Higher and Professional Education. It may be disapproval, approval with conditions, a request for additional information, or approval. The two institutions (Universidad del Noreste and Universidad Autonoma de Guadalajara) approved to date have both been approved with various conditions. Two of these conditions have been an ongoing monitoring of the institution's clinical clerks in New York State hospitals by department staff, and a reevaluation or site visit of the parent institution within a specified period of time.

In conclusion, the objectives of the New York State program to regulate clinical clerks from unregistered and unaccredited medical schools are being met. An effective system that clearly defines those conditions under which clerkships may be performed has been established. This system also exerts quality control measures over the educational experiences available to students. The use of the MSKP examination as a screening device provides directors of medical education as well as state officials with a mechanism for measuring student performance in the basic science areas after two years of medical school, and it provides at least an initial index by which to measure the student's beginning skills in introductory clinical diagnosis.

The system and criteria for the review of medical education programs located outside of the United States and Canada has had another positive effect. Through an ongoing system of program review, New York State is able to assure that students in selected unregistered and unaccredited medical schools are receiving a reasonable education. This has positive results for both the students and the citizens of New York State. In addition, the medical schools that have been evaluated have benefited from a process based on mutual cooperation and objective assessment. It should also be noted that detailed information concerning unaccredited and unregistered medical schools, which has never been readily available before, is now obtainable from the New York State Education Department. The availability of information concerning these schools, and the judgments that have been made based on reasonable standards and procedures are major steps forward in international medical education.

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PERFORMANCE OF U.S. CITIZEN-FOREIGN MEDICAL GRADUATES ON CERTIFYING EXAMINATIONS IN INTERNAL MEDICINE

The numbers and performance of foreign medical graduates taking ABIM [American Board of Internal Medicine] certification examinations during the 1975–1980 period were compared with those of their counterparts from U.S. medical schools. Among graduates of foreign medical school candidates taking their first examination, the numbers of U.S. citizen foreign medical school graduates have increased threefold and constituted 19 percent of all graduates of foreign medical school candidates taking the 1980 examination. In contrast, the numbers of all other first-taker graduates of foreign medical school candidates declined each year during the study period. It is likely that the rapid increase in U.S. graduates of foreign medical schools taking Board examinations will continue and perhaps accelerate in the future. The success rates of graduates of foreign medical schools on examination are low but have been improving gradually over the period studied, in contrast to higher and stable graduates of U.S. medical school pass rates. Approximately 80 percent of graduates of U.S. medical schools passed in 1980 on their first attempt but only 44 percent of all graduates of foreign medical schools passed. For all years studied, U.S. citizen foreign medical school graduate pass rates were lower than those of all other graduates of foreign medical schools, but the gap may be declining: 38 percent passed in 1980, the best result in recent years.

The findings of this study need to be extended by further work. Although it is clear that essentially all graduates of U.S. medical schools complete postdoctoral specialty training, is this also true for U.S. citizen foreign medical school graduates? Are those who undertake residencies and certification in internal medicine representative of all U.S. citizen graduates of foreign medical schools? An affirmative answer would lead to disturbing conclusions from their poor performance on these examinations. The significance of results of examinations should not be overinterpreted since they do not measure all the requisite qualities of an internist, but they do speak to the specialists' knowledge and problem-solving capabilities and appear to correlate with other components of clinical competence in internal medicine. Clearly the U.S. citizen graduates of foreign medical schools studied here are not as well prepared as their fellow citizens educated in U.S. medical schools. The reasons frequently put forth to explain the lower success rates of graduates of foreign medical schools (unfamiliarity with testing methods, language or cultural experience deficits) obviously do not apply to U.S. citizen graduates of foreign medical schools, but the study of medicine in a foreign language (as these U.S. citizen graduates of foreign medical school cohorts did) may be a disadvantage.

As U.S. citizens return from new foreign medical schools, the need for information about their career choices and success in meeting professional standards will become greater. One may not be able to extrapolate the results of this study to these future cohorts.

—JA BENSON JR
JA MESKAUSKAS
LJ GROSSO
Am J Med 1981; 71:270–273

Effects of offshore medical students on hospitals, medical schools, and physicians in New York State

RICHARD N. PIERSON, JR, MD

A tragedy, in the dramatic sense of the word, deals not so much with sadness as with the inexorable working out of events from a given set of initial conditions. A tragedy occurs when the stage is set in a particular way, and each of the characters behaves according to the rules that all the participants have agreed to observe. The issue of the offshore medical schools and their graduates is a classical tragedy, which may be of minor or heroic dimensions, depending on actions yet to be taken. In addition to the effects of these schools on the hospitals, medical schools, and physicians of New York State, it is inevitable that the tragedy will affect patients eventually, although these effects are more difficult to predict due to the insufficient data available.

Between 14 and 25 offshore medical schools contribute approximately 3,500 graduates each year to the pool of students that applies for residency training in American hospitals. The schools vary in size, curriculum, and preadmission requirements. Many students are admitted with advanced standing, whereas others transfer credits from one school to another. Admissions to the schools occur as often as three times a year. Students take and retake the examination of the Educational Commission for Foreign Medical Graduates (ECFMG), and it is sometimes difficult to determine the standing of an individual student. It would be inappropriate to assume that either all schools or all students within a school are similar, and it would be equally wrong to characterize any particular United States foreign medical graduate (USFMG) as being identical to the anecdotal best or worst example. However, it is necessary to develop a strategy to deal with the offshore medical schools as an entity in medical education in New York and other states, for the numbers of their students are too large to absorb, either as clerks or as newly licensed physicians, in New York State.

EFFECTS ON HOSPITALS

University and teaching hospitals experience minimal effects on their programs or their patient care, since applicants from American and Canadian medical schools will usually fill their clerkship and residency programs, and their staff members will be selected from graduates of their own or similar programs.

Community hospitals that have residency programs will be most affected by offshore students, because some of these institutions will be invited to offer third and fourth year clerkships to offshore students, under contract with the offshore schools. The nursing, medical and administrative staffs, and the trustees will each be affected if they accept these invitations. There are few drawbacks, such as possible increased exposure to risk via malpractice suits, but many advantages including paramedical staff, a stable of candidates for residency positions, and a "teaching hospital" image as well as fiscal benefits. For many years community hospitals have accepted foreign medical school graduates for residency positions—enjoying the accompanying benefits—while subsequently refusing to accept these physicians on their attending staffs.

The community hospitals are one of the most important pressure points of the evaluation and accreditation program concerning offshore medical schools of the New York State Board of Regents: if none offered to provide the clerkships, the Regents' program would be empty. To date, offshore schools have not had difficulty in recruiting a sufficient number of directors of medical education and in affiliating with community hospitals.

Proprietary hospitals and nursing homes are not affected by offshore clerks, except possibly when moonlighting clerks take laboratory or physician's assistant positions. These institutions may find future physician employees more readily, however, as FMGs add to the increasing physician manpower supply. In fact, it has not been established that offshore medical school graduates—or any other group of graduates—are more likely to take positions in understaffed, low-budget institutions, or in underserved rural or urban areas, once the necessary residency training is finished and licensure is in hand.

State mental hospitals and other chronic care institutions, as well as hospitals in rural areas and urban centers are difficult to staff and thus remain underserved. These positions are often filled by non-American foreign medical graduates, the most capable of whom leave whenever possible for mainstream opportunities outside of the disadvantaged areas. These institutions would benefit, at least in the number of applicants, if they could attract USFMGs. Neither experience nor logic suggests that USFMGs will apply for these positions by choice, for they are, if anything, more attuned than other foreign medical graduates to the advantages of mainstream positions.

EFFECTS ON MEDICAL SCHOOLS

The 12 American medical schools in New York State suffer no direct harm from an influx of USFMGs, since their own students will be far more competitive for residency positions, and few USFMGs will be found in university-

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Address correspondence to Dr Pierson, Director, Division of Nuclear Medicine, St Luke's Hospital Center, Amsterdam Avenue & 114th Street, New York, NY 10025.

affiliated teaching hospitals. However, at the clerkship training level, schools that require the use of additional hospitals must compete for access to patient care experience for students. Whereas the State University of New York (SUNY) College of Medicine at Buffalo has told its affiliated hospitals to choose between affiliations with offshore schools and SUNY,[1] not all schools have been able to be so direct, and loss of opportunities for contact with patients is a genuine risk.

American students will have a great advantage in obtaining clerkships, and subsequently in applying for residencies, with only the weakest United States medical students being less competitive than USFMGs from offshore schools. However, the prospect of choosing to practice in New York State will be less attractive if there are numerous other physicians opening practices in competition.

In the 1930s, medical licenses issued in Massachusetts were not recognized in many other states because of the existence in the state of the substandard Middlesex School.[2] A similar threat occurred with New York State licensees when an influx of European refugee physicians suggested a dilution of quality to licensing boards in some other states,[3] and a withdrawal of licensing reciprocity was threatened. Could this happen to New York State licensees because of the Regents' program?

EFFECTS ON PHYSICIANS IN NEW YORK STATE

Established physicians with stable practices will notice minimal direct effects from a small influx of USFMGs, no matter what the qualities of the new physicians. However a large influx—with as many as one in 10 graduates that enter residencies being USFMGs—could promote radical changes in the medical practice environment. At the other end of the age spectrum, young physicians seeking to enter private practice will be competing with many more FMGs, both US citizen and alien.

The data on which to base predictions of the effects of USFMGs on physicians in New York State are insufficient. They do, however, provoke a series of questions. Would health care become less costly with more competition? Would health care become more cost effective? Would malpractice risk, and therefore premiums, increase throughout the medical community because USFMGs covered by the same company were subject to more malpractice suits? Will hospital staff positions and community practice opportunities be so saturated by USFMGs (perhaps with "show cause" orders from courts) that there would be no new places for better qualified US medical school graduates trained in subsequent years? Will public expectations of physician competence and respect for physician ability lessen because of "quality dilution?" Will forged and sold licenses from offshore schools be more difficult to detect because of students' frequent transfer of credits and schools?

WILL LAW CONTROL MEDICINE?

USFMGs often qualify for Guaranteed Student Loan Programs to pay for the high cost of education in offshore schools.[4] Their rights as United States citizens extend much further than the loan programs, and pressures will inevitably arise to enforce other rights of equal access.

When an offshore medical school gains recognition and standing, lawyers will be engaged to challenge *any* restrictions placed on the school's rights to training procedures, licensure, access to hospital staffs, malpractice insurance, or indeed any other right that is decided by an "expert committee," a state board of education, for example. Law suits will be expensive to defend, because they will be brought and defended individually, rather than as "class action" regulations, such as a recent case in California, in which the California Board of Licensure ruled that no graduate of a certain school would be considered to have a medical degree.[5] That law suit has not been decided, but recent court practice has been more sensitive to the rights of the individual applicant than to the possible risk to society of relaxing the conditions for licensure.

Both the Federal Trade Commission and the state legislatures which, for example, have difficulty in defining the difference between chiropractic and traditional medicine—because chiropractors and physicians have identical constitutional rights—are likely not only to allow but to enforce equal access for any physician to diagnostic and therapeutic drugs and technological devices, regardless of the medical school of origin.

Flexner and many physicians and educators of his period suggested that a medical school could best be judged by its faculty, libraries, and laboratories, its association with a hospital, and ideally, its association with a university.[6] The American public of the late 19th century, concerned about the lack of controls for medical education, supported this position. The climate has changed radically, however, and the courts are likely to follow the policy of the Federal Trade Commission in favor of advertising and free competition. In this setting, success in the medical marketplace will be more a function of public advertising than of medical ability.

What defenses do organized medicine, medical schools, physicians, and hospitals in New York State have against the *de facto* definition of what constitutes a medical school and what constitutes the rights of a USFMG? Will the Regents' program make it easier for the graduate of an offshore school to sue for access to a residency program, for a license to practice, and for a position on a hospital staff? For now, only access to clerkship is guaranteed, but what argument will limit the expansion of access into the next levels of certification, based not on evaluation by peers or on national need, but on a citizen's rights of access?

The climate in which the Regents established their program has changed during the past three years. The oversupply of graduates from American and Canadian medical schools predicted in the Graduate Medical Education National Advisory Committee (GMENAC) report is approaching and the projections for overproduction are at least as serious as Tarlov initially suggested.[7] Furthermore, a reduced number of residency programs and positions has already assured most hospitals of having many applicants from American schools. USFMGs may have difficulty obtaining places.

The vulnerability of some offshore schools to Caribbean insurgency or to the suspicion that fraudulent degrees may be a greater risk than at American schools has aroused more public interest in the schools than any earlier concerns raised by American medical schools about the quality of education. The net effect of this publicity has probably been negative.

The evaluation program managed by the underfunded State Department of Education staff has moved slowly. Two schools have been evaluated, five more are under scrutiny, and at least 13 have not even applied.[8]

The net results of the forces engaged in determining the future of the offshore medical schools are unpredictable, and they may have passed beyond the power of the Regents to control the outcome. The results may, at worst, be determined primarily by the courts, which may focus more on the rights of individual applicants than on the needs or the rights of hospitals, physicians, patients, or of society. The Regents may have prepared for the USFMGs a case based on "equality," which will be judged by laypersons not previously trained or expected to judge medical quality. It is still within the power of the Regents to set minimum standards for the teaching capabilities both of the offshore schools and of the hospital clerkship programs in the state. There are few physicians or educators, except for those who benefit directly from the schools and their programs, who would make a case for the clerkships as being either logical or beneficial to the needs of hospitals, physicians, or patients in New York State.

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OFFSHORE MEDICAL SCHOOLS

The various host Governments are aware that the presence of a medical school will contribute to the economy: students and staff must be housed and fed, and visitors and relatives will also contribute. The medical school's contribution to the economy of Grenada has been said to be as high as 15%. The demand for housing by students and staff is not, however, always beneficial to the local population. On St Vincent, for example, the price of housing has been so inflated that local people have found it difficult to compete. The geographical situation of the schools is not conducive to cultural exposure. On the islands of Grenada and St Vincent, the cultural deprivation must be detrimental to personal development, unless medical students are expected to study their subject to the exclusion of all else. The climate is not always conducive to study, the breakdowns of the power supply may interfere with air conditioning and lighting. Political stability cannot be guaranteed with the ever-present possibility of civil or military commotion. The climate and facilities for enjoying outdoor pursuits in the Caribbean are, however, idyllic.

The costs of these courses are considerable: at St George's, tuition fees are currently about $3300 each semester, which amount to almost $30,000 for the four-and-a-half year programme. Students are responsible for their own living and travel expenses which can cost another $6,000 annually. About 190 students start the programme each semester but only about 150 continue with the course.

The medical training in St George's, which is one of the better schools, is along traditional lines with separate preclinical and clinical teaching. Practical anatomy is part of the curriculum but due to limited resources—including cadavers which have to be shipped in—much of the teaching is by demonstration. Each student, as a member of a team, actually dissects only one part of the body (limb, chest, head, and neck, &c). There seems to be no practical physiology, biochemistry, or pharmacology. Histology is mainly taught, with the use of 35mm slides and a viewing box; there is little microscopy. Morbid anatomy is taught, but there is no museum for study of pathological specimens. Despite these limitations, however, students do well in the American examinations. On the island of St Vincent, clinical training begins in the hospital of 250 beds. The facilities are limited, with haematology, biochemistry, and radiology well below the standards of today. To quote from the report of the U.S. General Accounting Office," equipment was minimal and much of it was inoperative". The introductory clinical course lasts one semester (6 months). Students are then sent to various institutions to spend the next two semesters in clinical study. Some come to the U.K., where several hospitals offer clinical training. The fourth clinical semester is arranged by the students themselves and may be in one or several units in the U.S., the actual specialty or specialties chosen by the student. A final semester is spent back on the islands of Grenada and St Vincent, where ". . . the chief of the hospital's medical staff said that the hospital was grossly inadequate for clinical training.". . .

Certain questions need to be answered, with particular regard to the supply and demand of medical practitioners. Considerable discussion surrounds the issue, but offshore medical schools seem to provide no answer. If more doctors are needed, then this is surely not the best way to train them; if no more doctors are required, then the schools are creating a glut. It has been argued that offshore schools can provide a training for students from countries where there is insufficient medical education. If this is required, surely the places can be provided by established schools. Another justification for the schools' existence is that the students are enthusiastic and well-motivated. These attributes must undoubtedly be shared by any group of young people following a course of study to which they are committed.

—FJ WOODROFFE
Lancet 1982;2:546–547.

Clinical clerkships

Problems and Solutions

JACKSON W. RIDDLE, PHD, MD

The Board of Regents and the State Education Department of the State of New York recently tightened the requirements for attaining clinical clerkships. Therefore, the following comments may be less applicable to New York than they would have been prior to the institution of these new requirements. Because of these more stringent regulations, many students from offshore medical schools will seek clerkships in other states that have fewer requirements or none at all.

Many physicians and hospitals are torn between their legal and professional responsibilities to protect the health and welfare of their patients, and their sympathy for and desire to help the students who attend offshore medical schools. Some of these dedicated and persistent students are willing to spend large sums of money to earn a medical degree. Other students who are not so dedicated or sincere pick the easiest and shortest route, either by moving from school to school or by buying bogus degrees and diplomas. They don't deserve our help. For example, recent newspaper articles carried stories of fake medical diplomas sold by four schools in the Dominican Republic to students and to others who paid from $5,000 to $50,000. Over 3,000 persons are under investigation in 15 states. How is one to distinguish between the students who should be helped and those who should be prevented from progressing through the system to actual contact with patients?

Anecdotal information and direct knowledge have contributed to a fairly accurate picture of the travesties of medical education foisted off on both unsuspecting and fully aware students and their parents by some offshore institutions that call themselves medical schools.

IMPORTANCE OF THE CLERKSHIP

Clinical clerkships for offshore medical school graduates are arranged through a variety of routes. They may be negotiated by the school with the hospital and the student; more often the student must make his own arrangements with a hospital that does not have an accredited residency training program or other teaching affiliation. There may or may not be some financial consideration involved. The levels of supervision and teaching, and the accuracy of documentation of the actual time spent in the clerkship with inclusive dates and a performance record of the student vary.

Overall, integration and coordination of the clerkships seem to be lacking. It is necessary to stress the importance of the clinical clerkship, because it is the equivalent of the entire third year of the medical curriculum in this country. If the student clerks in a small, understaffed non-teaching hospital, as many do, the clerk frequently becomes another pair of hands assigned to duties that contribute little or nothing to his medical education.

There is often little proof that the student spent the requisite amount of time in a productive educational experience, supplemented by clerkships distributed among the basic clinical specialities. What proof is there, for example, that the student who wants to become an obstetrician does not spend all, or a disproportionate amount of his or her time in that field, without proper instruction and clinical exposure to medicine, surgery, pediatrics and gynecology? Should the school accept the student's word for his clerkship experience?

During the clerkships the student will have direct contact with patients and will be allowed to perform certain prescribed procedures, some under supervision and some on his or her own. What are the risks for the patients? What are the risks for the hospital and for the preceptors? One poorly trained student could create a serious situation; multiply that risk by the thousands of students coming from the offshore schools, and the potential for harm is monumental.

Without dependable documentation of clerkship experience and performance, how can residency program directors and hospital administrators make informed and valid judgments concerning applicants to their programs of graduate medical education? And how can the state licensing board make an intelligent appraisal of the candidate's record without such documentation, when the applicant applies for a temporary permit or a license to enable him to pursue his graduate medical education? At the present time no acceptable and reliable evidence exists for thousands of students now in the offshore system.

QUALITY STANDARDS NEEDED

Some insist that the problems of the offshore medical schools will disappear gradually because of two factors: the decreasing number of qualified applicants to United States medical schools, and the shrinking numbers of available positions in residency training programs. In my opinion it will be a long time before these factors bring about the demise of the entrepreneurial offshore schools. Certainly the vicissitudes understood and experienced by both the schools and students have not served as a deterrent to either.

As long as the offshore medical schools maintain a large population of students from the United States, controls

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Dr Riddle is a consultant to the Medical Society of the State of New York.
Address correspondence to Dr Riddle, 777 N. Michigan Avenue, Chicago, IL 60611.

must be established to assist deserving students in gaining a satisfactory basic clinical education and to prevent the less competent students from entering the American medical system. The offshore medical schools could establish criteria and requirements for clinical clerkships that would have educational standards, evaluations, and documentation comparable to those required by accredited US and Canadian medical schools. Based on their performance to date, however, it seems unlikely that they can or will do so. It would require expensive, time-consuming negotiations with teaching hospitals, preceptors and program directors whose facilities and time may be saturated with students from accredited medical schools. Supervision, compensatory lectures, demonstrations and conferences would be required to bring these students up to the level of third-year American students. Distances of hundreds or thousands of miles that separate these schools and the cultural and language differences make this task even more difficult.

The World Health Organization (WHO) could tighten its requirements for the listing of institutions in its *Directory of Medical Schools.* For example, it could restrict listings to those schools that educate only students who will practice in that country, or if that is too restrictive, perhaps only list medical schools in which 95 percent of the students will practice in that country. It is my understanding that the criteria for listing in the WHO *Directory of Medical Schools* are now being reviewed and are subject to revision.

The American Medical Association recently conducted a nationwide survey regarding possible state regulations on clerkships for students from foreign medical schools. Ten states have such regulations: California, Idaho, Indiana, Louisiana, New Hampshire, New York, New Jersey, New Mexico, Pennsylvania and South Dakota. Maryland and Texas are in the process of developing regulations. Six states have a simple regulation stating that clerkships must be taken only in teaching hospitals. New York and California have much more elaborate rules.

California's regulations apply both to the student and to the kind of institution that can offer clinical training programs for foreign medical students. The regulations are very restrictive, pertaining to the qualifications of the hospital as well as those of the program director. Idaho restricts clerkships to students from an "acceptable school of medicine" who must be registered under the State Board of Medicine after filing a verified application. Pennsylvania flatly forbids all clinical clerkships for foreign medical students.

The council of the South Dakota State Medical Association directed that the policy of the hospital of the University of South Dakota—that it will not accept students from non-accredited medical schools—be disseminated to other hospitals in the state for their consideration and information. Other institutions have made individual and independent decisions, such as SUNY-Buffalo which warned its affiliated hospitals that they would lose their academic affiliation if they accepted foreign medical students as clinical clerks.

The Federation of State Medical Boards has not taken a position on clinical clerkships for foreign medical students and is not likely to do so. Any such action would have to be ratified by laws or regulations in each state. The Education Commission for Foreign Medical Graduates (ECFMG) is strengthening its examination of medical knowledge, the Foreign Medical Graduate Examination in the Medical Sciences (FMGEMS), to make it more comparable to the National Board Examinations. (1984 Information Booklet and Application, Foreign Medical Graduate Examination in the Medical Sciences (FMGEMS) and ECFMG English Test, Educational Commission for Foreign Medical Graduates, 3624 Market St, Philadelphia, PA 19104.)

The Association of American Medical Colleges and the Liaison Committee for Medical Education are concerned about the impact of clinical clerks from offshore schools on US hospitals; however, these bodies have no jurisdiction over foreign medical schools or their students and so are constrained from taking any official action.

The American Hospital Association (AHA) has expressed interest in the clerkship problem and is concerned about the potential hazards to patients and to its member hospitals. In 1983 the AHA conducted a survey of teaching hospitals regarding clerkships. Of the approximately 800 teaching hospitals that responded, 243 indicated that some form of clinical training was provided to students from foreign schools. The majority were voluntary hospitals or were controlled by state or local governments. Most were located in the large metropolitan areas of the eastern part of the country.

In August 1983, the AHA applied to ECFMG for a grant to conduct a survey of 6,000 hospitals, asking if they offer clinical training to undergraduate medical students from foreign schools. Those hospitals that respond affirmatively would be sent a detailed questionnaire, the results of which would be analyzed and merged with data from AHA's Annual Survey of Hospitals to determine the characteristics of institutions that offer clerkships to foreign medical school graduates. ECFMG awarded the grant in late fall of 1983, and the initial survey was mailed in April. The Department of Health and Human Services of the Federal Government has shown interest in this project and may grant monies to support site visits to the foreign schools as well as to certain hospitals offering clerkships. An accurate determination of the nature and extent of this practice would be of value to health policy planners in determining whether clerkships should be improved or curtailed. It would also provide valuable information to the ECFMG which must certify foreign-trained physicians for entry into graduate medical education in the United States, and which needs standards with which to judge the accuracy of this aspect of their medical education.

A set of precise requirements applicable to all students from unaccredited medical schools is needed. These would first document the student's eligibility to enter a clinical clerkship—satisfactory completion of two years of basic medical science education in a medical school, as documented by an official transcript and validated by an appropriate examination; and second, they would document each clinical clerkship taken by the student with inclusive dates, the speciality involved, the names of the preceptor and the hospital, and an assessment of the student's performance. The student's clerkship records would be submitted by the hospital(s) in which he or she studied; they would be collected and collated, and transcripts of these educational experiences would be sent, upon request of the applicant, to the school awarding the medical degree and to residency program directors and state licensing boards.

THE ROLE OF THE ECFMG

The Educational Commission for Foreign Medical Graduates is an ideal organization to develop and administer a regulatory program. It is a national organization with a governing board composed of well-known and respected medical professionals and lay persons. It combines the advantages of expert knowledge and experience in foreign medical education and credentials, adequate computer facilities, knowledgeable legal counsel, and a trained, intelligent staff. Its sponsoring organizations include the Association of American Medical Colleges, the American Board of Medical Specialities, The American Hospital Association, the Association for Hospital Medical Education, the American Medical Association, the Federation of State Medical Boards, and the National Medical Association.

The ability of the ECFMG to award or to deny certification provides the necessary clout to ensure compliance. The ECFMG requires official documentary proof of citizenship, undergraduate education, medical education, and the passage of an examination that tests medical knowledge and the comprehension and use of the English language. The commission may then issue a certificate that enables the foreign-trained physician to apply for entry into an approved program of graduate medical education in this country.

Because clinical clerkships are the integral core of the undergraduate medical education experience, and because the clerkships are obtained at different times in different hospitals and under several preceptors, it is logical to add the requirement of clerkship documentation, and verification by the hospitals involved, to the other requirements for ECFMG certification.

Such a requirement would not intrude upon the school's authority over its curriculum. It would simply record and transmit evidence of the clerkship experiences. This could be accomplished with a minimum of additional staff and commitment by ECFMG. Furthermore, it would assist the deserving, honest student, and also protect patients and hospitals from those who are not qualified.

I am pleased to report that a delegation from the Medical Society of the State of New York and I presented this proposal to the officers of the ECFMG in December 1983 for their consideration. It was placed on the agenda of their Board of Trustees at the April 1984 meeting. At present the proposal is under active study by the ECFMG.

SYRACUSE UNIVERSITY COLLEGE OF MEDICINE

Entrance Requirements. Two years of a recognized course in arts or in science in a registered College or School of Science which must include Latin, German, Physics, Chemistry and Biology. Six and seven years' combination courses are recognized.

The first two years are spent in mastering by laboratory methods the sciences fundamental to clinical medicine.

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NY State J Med 1923; 23:xiv

Offshore medical school graduates—a view from the New York City Health and Hospitals Corporation

Jo Ivey Boufford, MD

The New York City Health and Hospitals Corporation (HHC) is the largest municipal hospital system in the United States. As the official public hospital system for New York City, the HHC system consists of 11 acute care and four long-term care hospitals, four freestanding neighborhood family care centers, and more than 30 community-based medical and mental health centers. The hospitals of the HHC provide about 20% of all the inpatient care in the city. In 1983 this amounted to over 3.2 million patient days. That same year the HHC provided 4.4 million outpatient visits and 1.3 million emergency room visits, amounting to more than 40% of ambulatory care visits in the city. In some communities, HHC facilities are the only providers of certain services such as emergency and psychiatric care, alcohol and drug related treatment programs, outpatient facilities and long-term care for the hard to place. The HHC is committed to the maintenance of these special programs in addition to its more general mission of providing care, regardless of ability to pay.

GRADUATE MEDICAL EDUCATION AND THE HHC

HHC contracts with medical schools, teaching hospitals, and, in two cases, with professional corporations for physician and technical professional supervisory services at all of its hospitals and at many of its freestanding facilities. Even in those hospitals in which the HHC pays attending physicians directly from its payroll, rather than through the affiliation contract, selection decisions and professional supervision are provided by the affiliate because the chiefs of service are affiliate employees.

All residency recruitment, selection and training in HHC hospitals is performed by the affiliate as part of the contract, although virtually all of these residents are on the HHC payroll. Medical student training is conducted under the auspices of the affiliate for its own students and for students from other educational institutions through formal agreements.

Whereas the HHC supports the training of residents and the education of students because it enhances the environment in which services are delivered, resulting in better patient care, the corporation is not in the medical education business. The HHC can request increases or decreases in the numbers and types of residencies that will be funded in its hospitals, by shifting resources within the affiliation contract.

Although the HHC is limited in its ability to influence residency selection, its hospitals are at risk for the negative effects of programs that are not strong enough to attract adequate numbers of qualified applicants. In addition, as residency review committees scrutinize residency programs more closely, especially those in surgery and obstetrics and gynecology, pressure is being brought to bear to decrease program size and to consolidate into fewer training sites, and penalties are being imposed on programs that have high percentages of foreign medical graduates. Will necessary cutbacks or consolidations occur at the expense of municipal hospitals?

FOREIGN MEDICAL GRADUATES IN HHC RESIDENCY TRAINING PROGRAMS

Historically, the hospitals with the greatest dependence on foreign medical graduates (FMGs) tended to be located in the economically depressed sections of the city. This is no longer the case. The predominant characteristic of these hospitals is their tendency to have residencies that are not integrated with those of the affiliated medical school or teaching hospital. In other words, the residency is affiliated, but the residents spend most of their time at the city hospital, as opposed to the integrated residencies in which equal time is spent between the affiliated and the city hospitals. There are few FMGs in integrated programs regardless of the location or characteristic of the municipal hospital. System-wide FMG dependence varies with specialty, tending to be the highest, as a percentage of all positions, in core specialties such as pediatrics and lowest in surgery. Problems continue in areas such as rehabilitation and pathology, and are decreasing in anesthesiology. These trends are similar to the national patterns of shortages in various specialties. There are, however, exceptions to both of these patterns.

Another trend has been a steady decrease in the percentage of alien FMGs compared to United States foreign medical graduates (USFMGs). In 1980, 60% of all FMGs were alien FMGs, compared to 54% in 1982 and 49% on July 1, 1983. This shift was especially evident in post graduate year 1 (PGY-1) positions for 1983 in which 35% of the entering class were FMGs, evenly distributed between alien FMGs and USFMGs.

HHC's concern over foreign medical graduates began with the change in the Immigration Law of 1976 that restricted the flow of alien FMGs into the United States and required special waivers to allow alien foreign trained physicians to take residency positions in the United States. The concern at that time was of not being able to fill resi-

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Address correspondence to Dr Boufford, Vice President for Medical and Professional Affairs, New York City Health and Hospitals Corporation, 125 Worth St, New York, NY 10013.

dency positions in the HHC system without this pool of applicants and its potential impact on services. During 1977 to 1978, the corporation paid directly for 2,615 housestaff positions of which 1,122 (43%) were held by FMGs.[1] In 1981, an HHC Committee on Foreign Medical Graduates conducted a survey and found that 45% of 2,983 housestaff positions were filled by FMGs. The national average at that time showed that 16% of housestaff were FMGs. States with the highest percentages of FMGs in residency training averaged 25%, which was true of New York City as a whole.[2]

This committee made several observations about the nature of the corporation's dependence on FMGs, and these observations are still accurate. The number of FMGs is uneven across hospitals and across specialties. When the percentage of FMGs was tallied in 1977–1978, the range across hospitals varied from 89% to 17%. In the 1980 review, a similar pattern was found in which about one third of the hospitals exhibited little or no dependence on FMGs, a third were overwhelmingly dependent throughout the entire hospital and the rest showed dependence in only a few specialties. The 1982–1983 pattern revealed that of 2,355 housestaff positions on the HHC payroll, 33% were held by FMGs. The range among entering PGY-1 students was from 2% to 87%, although in only 3 of 11 hospitals were more than 50% of such positions occupied by FMGs.

Waiver requests have decreased from more than 200 in 1979—40% of the number requested throughout the country—to four in 1983. In this sense the problem of alien FMG dependence has virtually disappeared. The issue remains, however, of maintaining the largest number of qualified residents in the HHC system, FMGs or US medical graduates.

The overall decline in the numbers of residency positions and the increasing numbers of American graduates applying for these positions have caused a steady increase in the number of US medical graduates in the HHC system. Some HHC hospitals have preferentially recruited USFMGs, proposing that as a group they are stronger candidates than the American graduates that HHC hospitals can attract in competition with other New York City hospitals.

Certain hospitals have looked to other alternatives to address the problems of resident recruitment. One institution has developed a formal relationship with the New York College of Osteopathic Medicine and has been certified as an osteopathic student training site. It will eventually begin taking osteopathic residents or recruiting osteopathic students into its medical residency program. Another approach has been to increase the employment of non-physician providers in HHC facilities—physician assistants, midwives, and nurse practitioners. While this has not been pursued at the expense of residency slots in established programs, the HHC is using this approach at new facilities such as the Woodhull Hospital and Mental Health Center in Brooklyn. This model is more expensive, but the non-physician providers have proven to be very effective.

HHC POLICY REGARDING FOREIGN MEDICAL GRADUATES

While the situation is improving, there is still concern for maintaining a full complement of qualified residents for positions in the HHC system. Therefore, it would be premature to close off access to foreign medical graduates unless and until other more fundamental reforms are adopted to improve the availability of physicians and other health personnel in the primary care specialties and in the medically underserved communities such as those served by the corporation's hospitals and health centers.

There have been cutbacks in federal support for the educational initiatives taken since 1976 that address specialty and geographic imbalances in physician supply and reductions in the availability of paid positions for National Health Service Corporation (NHSC) recipients in practice settings. Thus, individual states will have to initiate programs to address these problems, and medical schools will have to use their influence to affect the types and locations of physician providers. There is evidence that the diffusion or "trickle down theory" is no more effective for physician distribution in socioeconomically deprived areas than it is for dollar distribution in these communities.

Concern about the quality of students or physicians trained abroad can best be addressed at the residency level and in the hiring of salaried physicians. It is the responsibility of the teaching hospital or health facility to select the strongest candidates from among the pool of applicants. A larger pool may offer better prospects to those institutions that are, for reasons of location or resources, at a disadvantage in recruitment.

The most cogent argument against state support for foreign medical schools or special arrangements for clinical training of these students seems to be its effect on state medical education resources. A bill has been proposed in New York State that would require a reexamination of the state's approach to its financing of medical education. The bill supports increased availability of primary care physicians in underserved areas. The role that state medical schools decide to play in regard to these reforms is critical.

MEETING FUTURE HEALTH CARE NEEDS IN PRIMARY CARE

There is evidence in the literature that explicit attention to the selection of medical students and residents and the experiences that they have in their medical education years can influence their choice of specialty and where they will practice—in this case in the direction of primary care and underserved areas. National data show that women tend to enter primary care specialties and tend to locate in underserved areas in greater proportion to their numbers than men. Similarly, minority physicians tend to locate in underserved areas to a greater extent than their Caucasian counterparts, especially in those communities with large minority populations. A concerted effort to encourage and support women and minorities to enter and complete medical school and residency training would take advantage of these inherent trends. A recent study of 11 primary care physicians in medically underserved areas in the Bronx demonstrated that those physicians who are based in institutional settings—hospitals and neighborhood health centers—in high need areas show a greater desire to serve a particular population, especially an ethnic group, than their counterparts in low need areas.[3] This kind of motivation should be explored during the medical school and residency selection process.

An evaluation of students that complete community and family medicine clerkships shows that these students tend to select family practice residencies. Some state schools such as Michigan State University and the University of New Mexico have undertaken major curriculum reforms to promote continuing primary care experiences for students in medically underserved areas in an effort to meet identified state health personnel needs.[4] Residency programs in New York City that stress experience for residents in primary care in medically underserved inner city areas have resulted in over 60% of these residents practicing in high need areas. Education can have an influence.

State financing incentives should support those medical education institutions that seek to encourage student and resident selection and educational program directions that are consistent with the desired health personnel policy. The HHC has assisted in the development of increasingly attractive primary care practice opportunities in medically underserved communities through reorganization of its ambulatory care programs and development of interdisciplinary case management systems. Coupled with the academic affiliations offered by medical schools and formal relationships with teaching hospitals for specialty support, such settings can make attractive practice opportunities. General improvements in the reimbursement for ambulatory care services, such as increasing the Medicaid allowances for physicians and freestanding facilities, are critical if primary care practice is to become more attractive and economically viable.

As the largest public hospital system in the country and the major provider of health services to the poor and minority populations in New York City, the HHC supports a health personnel policy that is committed to identifying and developing a cadre of excellent physicians regardless of their educational origins. A policy to limit the numbers of physicians in New York State cannot be developed without consideration of the need for physicians and other health care providers in certain specialities and locations. An effective program to address these concerns will require a careful balancing of the public interest with the interests of the medical profession and the institutions that provide medical education for the physicians of the future.

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Commercialism in medicine

Alan Blum, MD

The phenomenal rise of the offshore medical schools forces an examination of two major issues: the selection process for medical students in the United States that has made admission to medical school an end to itself; and the commercialization of health care that has distorted the image and role of the physician.

A decade ago, the dean of admissions at an American medical school admitted that of each entering class of 100 students, about half, in his opinion, were clearly outstanding and easy to select, even from over 2,000 applicants. The other half could have been selected by a lottery. But these proportions have changed today because of the declining numbers of students applying to medical school. When one considers the vagaries of computers and the impersonality of a mass-produced application system, one cannot help but sympathize with the rejected applicants, and perhaps also with the dilemma faced by deans of admissions.

In 1980 I wrote a commentary for *JAMA* entitled, "Who shall study medicine in the 1980's?" (244:779–780) in which I suggested that one solution to the admissions predicament would be to place a stronger emphasis on demonstrated community involvement; that is, what one has done to serve his or her fellow man before applying to medical school. This seems a more appropriate criterion than the fraction of a difference in grade point average or a slightly higher score on the Medical College Admission Test. Much of the discomfort over the issue of selecting medical students arises because nearly all applicants, be they scholars of science or the supposedly more well-rounded humanities majors, appear academically qualified on paper. Additional unease results from having to compare uniformly high grades from many colleges.

The response to the commentary was eye-opening. Some correspondents damned the idea as smacking of the Cultural Revolution in China, when medical school admissions were stacked heavily in favor of right-thinking but undereducated peasants over qualified middle estate applicants. One cynic wrote that the selection process is hindered by the fact that the American applicant to medical school is the product of a distinctive socioeconomic order where monetary gain is prized above human attributes such as dedication, love, friendship, loyalty and personal integrity. Service to mankind, the writer continued, is not a motivating force in our country for those seeking to enter the practice of medicine. He even condemned the suggestion that there be required courses in medical ethics, pointing out that character building should be a part of childhood development. In the United States, he concluded, character building is a neglected art, and, in fact, one of only historic interest.

Another irate letter writer noted that his medical school had selected an individual in large measure because of his outstanding record of community involvement, only to learn two years later that the student was a convicted felon who had been sentenced by a judge to "serve his community." A similarly dismissive correspondent reminded me that community service is not the physician's *raison d'être*. Most physicians' primary responsibility, he wrote, is the care of sick patients, and the vast majority of physicians' time is spent taking care of patients or related work.

My response was that from this decade forward our enormous knowledge about preventing illness and our capability to communicate it through the mass media and in our offices and hospitals means that being a healer of the sick no longer constitutes the complete role of the physician. By definition a physician has always been and will forever be a teacher, whether of an individual patient and family, or of one's colleagues, or of the community-at-large. Paramount to being a good physician is possessing skill in communication, an ability that needs to be acquired early on, well before medical school (or residency where most training takes place today). Communication skills must be honed unendingly and mainly in the context of integrating with one's community. It would be marvelous to require first year students to walk to school or to travel by mass transit and thus to meet and talk with people in the surrounding community. The skills of listening to patients and talking with them are hampered when one's relationship to the community is restricted to a hospital, clinic, or classroom setting. Are medical schools serving their communities as well today as half a century ago when students made home visits, lived in the neighborhood, and were a part of the community themselves?

Responding to my concern that we may be discouraging the most compassionate and humane students from applying to medical school by the competitive means-to-an-end approach and focus on science, one medical student wrote that the fault in losing compassionate individuals does not end with admissions policies; rather, that is where they begin. I had written that to be a humane physician one must first be a humane person. But it was this student's belief and observation, as he neared the end of his medical school years, that one is more humane before medical school than after. He noted how medical students are taught to hide their feelings rather than express them; and when they do express compassion toward their patients, they learn to do it in a contrived and superficial way, rather than with spontaneity and genuine feeling. It is no coincidence, he observed, that for many a "professional" attitude has become synonymous with a cold and matter-of-fact approach.

I believe that neither the offshore medical schools nor most of the 127 mainland medical schools are imparting forward-looking priorities for physicians. By and large, medical schools are not challenging commercialism or en-

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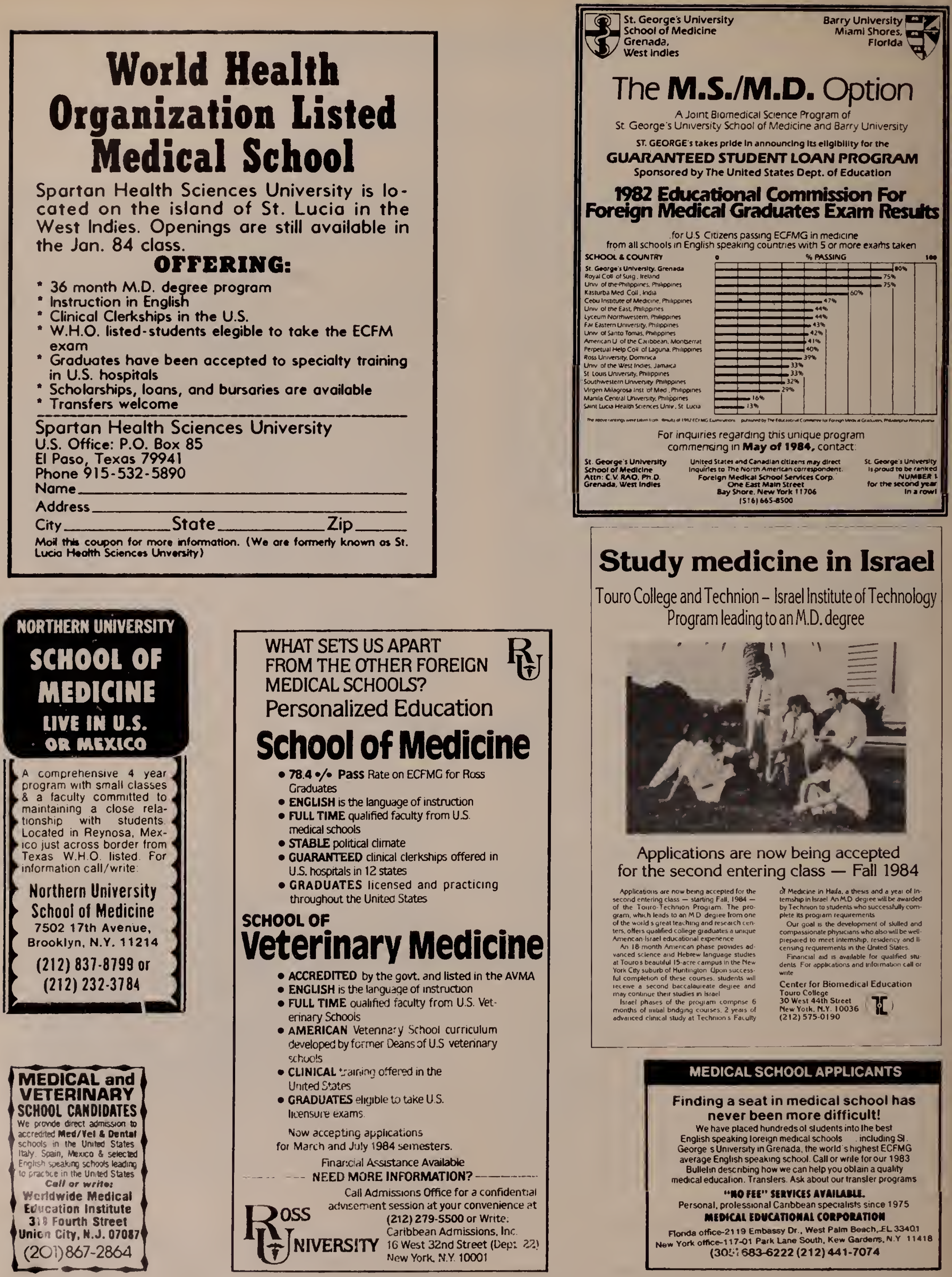
Address correspondence to Dr Blum, Editor, *New York State Journal of Medicine*, 420 Lakeville Rd, Lake Success, NY 11042.



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- American curriculum/American & British faculty members
- 90% of 1981-82 AUC'S American graduates have passed the ECFMG qualifying examination
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couraging social awareness. To the contrary too many are caught up in commercial self-interest, placing greater emphasis on gaining research grants, forging profit-making ventures in biotechnology with outside vested interests and expanding lucrative diagnostic and therapeutic facilities than on teaching students, deemphasizing subspecialization, or improving the health of the community as a whole.

The more one looks at the offshore schools, the more one sees deficiencies and complacency in the "onshore" schools. Offshore schools may simply be doing no worse than the others. There are countless reasons to criticize the offshore schools: their profit-making objectives, lack of bedside teaching, irrelevance to the community, meager laboratory training and absence of full-time faculty. T-shirts, jeans, and sandals are the manner of dress of the largely white, upper middle class students. Rather than studying for the joy of learning or to impart knowledge to others, they train to pass examinations. But are not such criticisms applicable to many American medical schools? The notion that offshore schools sell admissions hints of the worst form of commercialism, but can this practice be said to have ended at schools in the United States? And is it not ironic that some physicians opposed to the concept of medical education at the offshore Caribbean schools see nothing wrong with taking a continuing medical education course as a tax write-off holiday on a Caribbean island or cruise ship?

If the proliferation of offshore schools in recent years is to be condemned, then what of the proliferation of American schools of the past decade? At least part of the origin of this boom lies in the widely disseminated report *Higher Education and the Nation's Health*, released in 1970 by the Carnegie Foundation, that warned of a physician shortage. Written by a committee of 19 persons that did not include a physician, the report called for a 50% increase in the number of medical school entry places by 1980 and the shortening of the medical school curriculum to three years. Glossed over were a consideration of enhancing existing resources and better disseminating knowledge of preventive medicine. No self-respecting commission on health care in an activist era should have omitted mention of drug abuse, smoking, automobile deaths, violence, and environmental health, but this one did. To the Carnegie Foundation committee, the main component in the solution of an impending health care crisis was the churning out of more MDs more rapidly.

Many in government took these recommendations seriously. The end result was a rapid expansion of class size at many medical schools and the establishment of new medical schools in the United States. This expansion was fueled by federal and state capitation grants and other incentives to increase the numbers of medical school graduates. It has now created a physician surplus.

Despite the enormous expansion of medical schools in the United States, many applicants were still unable to gain admission. Large numbers of the "baby boom" generation placed the same kinds of pressures on medical schools that they had previously placed on all levels of education from kindergarten through college. Even the expansion of the American medical school system could not accommodate them. This created a large pool of disappointed medical school applicants, which private entrepreneurs in the Caribbean and Mexico quickly satisfied by establishing profit-making medical schools.

The invasion of Granada catapulted the offshore medical schools into prominence. Whereas the kindest things that had been written about these schools were that they were "struggling" or "troubled" or "controversial," their medical students became overnight heroes and martyrs in the mass media. What other group of medical students has been invited to visit the White House? Suddenly a host of American institutions were offering their facilities to the beleaguered students. In *The New York Times*, advertisements for the offshore schools increased in size and frequency. (In spite of *The Times'* having helped reveal some of the diploma mill practices in the Dominican Republic and elsewhere, advertisements for offshore schools have continued to appear, unchanged.) To be sure, such ads do recall similar appeals for applicants 50 years ago in the *New York State Journal of Medicine* for medical schools such as Buffalo University, Syracuse University, and New York University? And is advertising for offshore medical school opportunities different from the advertising by an increasing number of physicians in the Yellow Pages, on billboards, in newspapers, or on television and radio? After long-standing opposition to such self-promotion, are not medical associations beginning to aid physicians in "marketing" their practices?

I wonder if the offshore schools, like so many slick throwaway medical magazines, are not merely capitalizing on the commercialism that pervades our society and our health care system. Are the advertisements for the offshore schools—including a videotape sales pitch by actor E G Marshall and nightly commercials on a popular radio talk show—different from a television advertisement for a political candidate, a chiropractor, a hospital alcohol treatment facility, a Park Avenue plastic surgery center, a cataract specialist, or an enuresis "institute?"

For the foreseeable future, a glut of physicians, produced in part by the offshore schools, is likely to lead to increased competition for the health care dollar and a rise in commercialism. It is also possible that medical schools will place greater emphasis on communciation skills, will devote more serious attention to both individual and community-based preventive health strategies, and will instill in students the image of the physician as teacher and civic leader, not just as a prescriber and technological miracle-worker. For this to occur, medical schools will have to reassert independence from commercial interests, place a premium on full-time teaching, and involve students in the community throughout their training.

Providing clinical clerkships for Americans from foreign medical schools

Alvin I. Kahn, MD

Teaching hospitals should consider two questions when assessing clerkships and educational resources that could be made available to foreign medical students: Should we make a special effort to aid these students? Can we afford to allocate resources to them? Decisions should take into account many diverse factors including university commitments for training American students, standards of eligibility, finances, and institutional resources for quality education.

One who has not undergone the experience cannot appreciate the life of a student in a foreign country. I remember as if it were yesterday my thoughts shortly after arriving in Bern, Switzerland. I gazed at the high ceiling in my *pension* and wondered if I could survive five years as a foreigner. My terrorizing frustrations as a medical student in Europe were first experienced the following evening when I attempted to read a chapter in a German anatomy text. By midnight, I had succeeded in finding one English word for each German word in the first paragraph—I still had no idea as to the meaning of the introductory statements. By the end of the first week my American colleagues and I had memorized enough German words, better at this point referred to as "nonsense syllables," to perform creditably on our first oral examination.

Should We?

Uppermost in my mind in considering this question is a simple principle: It is correct to recognize exceptional motivation in a student, when this is combined with a documented satisfactory academic performance. Acceptance into American medical schools is fundamentally an award for academic excellence during the undergraduate years. Desirable candidates usually present a near-perfect grade point average, excellent Medical College Aptitude Test (MCAT) scores and a striking personal interview before the admissions committee—all supported by a commitment to community service. A review of current medical school applications indicates that volunteer ambulance service should begin shortly after nursery school, and a major Himalayan expedition should be undertaken as a teenager; research of Nobel prize caliber should be completed in undergraduate school. When one ponders such expectations, it is interesting to note how dissatisfied the public appears to be with the final product. It is even more sobering to consider the qualifications that are required for a profession that is increasingly dependent on sophisticated technology and is becoming increasingly specialized.

Two other aspects of American medical education are assuming greater importance. First, financing this venture has become formidable; the debt on graduation may exceed $100,000, in addition to living expenses and the cost of establishing an office and obtaining insurance.

A second factor is the need for scientists who can help support university programs with grant monies. The era of the great clinician-teacher has come to an end. When asking a first-year resident, "Who taught you in medical school?" I have yet to hear as a response the name of a department chairman. I was privileged to be the student of four great teachers: Walter Frey, Walter Hadorn, Daniel Laszlo, and Isidore Snapper. They made me feel part of a medical tradition; through them, I was only a hair's breadth from Pel, van den Bergh, Virchow, Fick, Sahli and Freud, and not far removed from Hippocrates. I at least knew about the Hippocratic revolution and its effect on the earlier Cnidian school of medicine. Frey developed the use of quinidine as an anti-arrhythmic agent. He visualized the teaching of medical students as part of a great drama. Hadorn added a global perspective to teaching. To this day, it is very emotional for me to read his farewell address to students and colleagues, which concluded, "I hope that you have learned much from me, not merely how to be good physicians—that is too easy—but how to deal with your professional lives as responsible human beings."

Laszlo was a pioneer in oncology. Aside from outstanding clinical ability, he taught us how to deal with mistakes, always maintaining our dignity and sense of integrity.

Snapper was the consummate teacher, in many ways the greatest of all, because students remembered so much of what he taught. A year of his teaching provided a permanent wealth of material that never again had to be reviewed. Snapper selected from his vast medical repertoire only important material, repeated it over and over again, and surrounded his clinical presentations with anecdotes that imprinted the essential points in one's memory forever.

I cannot conclude an appeal for humility in assessing the American system of medical education without mentioning the high degree of disorganization of third- and fourth-year curricula. Such programs encourage premature pressure to specialize, fail to provide students with a clear understanding of the philosophical basis of medical science and practice, and fail to integrate modern technology, ethical considerations, legal principles, cost containment, quality assurance, utilization review and diagnosis related groups into the body of knowledge required upon entering into the American hospital system. There is also a contradictory

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Address correspondence to Dr Kahn, Director of Medical Affairs, The Brookdale Hospital Medical Center, Linden Blvd at Brookdale Plaza, Brooklyn, NY 11212.

approach to research, in that while acknowledging its importance, no attempt is made to teach research techniques, the evaluation of papers, or an overall assessment of current trends and their significance.

Even the basic course on physical diagnosis, which offers an opportunity to underscore the traditional and unique right of the physician to see and deal with a body as a whole, leaves students with a great sense of inadequacy. All too often the course is taught by many different specialists. This is a subtle way of saying that no one physician could or should conceive of performing a good physical examination. Emphasis should be placed on the fact that physical diagnosis is difficult and only years of patient, dedicated observation will allow the accumulation of enough experience to use its techniques with confidence and accuracy.

What could foreign students add to our medical institutions? First, the sheer numbers of these students force us to evaluate the current system of education. Second, foreign medical students may inspire other students with their maturity, exceptional motivation, enthusiasm, and experience with a different culture.

CAN WE?

Can we accept these students without compromising our own limited resources? Can we compensate for inadequacies resulting from educational deficiencies and marginal entrance standards? This could be achieved by working with university-affiliated hospitals with approved residency programs, following an assessment of the student's abilities and potential. When accommodating students from foreign medical schools, however, students in United States schools should not be compromised.

Several conditions must be met in order for students from foreign medical schools to be integrated effectively into the American medical system. Foreign medical students should not be used to fill deficits in personnel—particularly at the resident level. They should be assigned to institutions with substantial teaching resources that could provide them with a variety of contacts with patients, capable residents who enjoy teaching, and preceptors who are enthusiastic about passing on the empirical knowledge and traditions that form the basis of the medical profession.

It is not desirable for a hospital to accept students from many different foreign medical schools. The principle of one hospital/one school would allow for curriculum development, uniform standards of student acceptance, faculty exchange, and educational research. Implicit in such an arrangement would be the possibility of failure on the part of a student who demonstrates substandard performance during a clerkship or subspecialty elective. The hospital should accept its responsibility of functioning as a university, particularly with respect to handling credentials and final evaluations.

Foreign medical students should not be sequestered from their American counterparts. Our healthy appreciation for the plight of the underdog has served all walks of American life. It is only through these contacts that foreign students can evaluate their progress as physicians-in-training.

Frequent in-depth reevaluation should always be a requirement, since all areas of medical education can benefit from review and change.

CONCLUSIONS

If Americans in foreign medical schools are ignored, two rather ugly consequences may result: (1) their numbers will constitute a political force, imposing political solutions on the profession; (2) a subgroup of physicians lacking proper credentials will come into existence and somehow find their way into our health system, having no loyalty to and no possibility for discipline by the profession.

Those offshore schools that have exhibited a true interest in developing universities capable of training physicians to meet designated standards of the United States system, such as the Universidad del Noreste and the Universidad de Guadalajara, should be encouraged in pursuit of these goals.

It is not within the character of a physician to limit compassion only to the sick. Although there are problems with medical education, they can be resolved if placed in proper perspective and approached with an eye toward the future.

The US foreign medical student and New York State: a study in controversy

BARRY STIMMEL, MD

Although the number of applicants to United States medical schools has been declining slowly over the past decade, there were more than 17,250 students unable to gain admission to the class entering in 1983.[1] Among those students wishing to become physicians are a disproportionate number of New York State residents—10.4% of all applicants. New York State, with 10% of the nation's medical schools, ranks first in the number of available first-year positions. Its four state universities, enrolling over 90% New York State residents, and its eight private schools, enrolling up to 70% New York State residents, are still not able to accommodate all of those students in the state who wish to be physicians. Each year there are more than 1,000 New York State residents unable to gain admission either to a school located within New York or to another medical school in the United States.

Many of these students, maintaining their commitment to medicine, enroll in foreign medical schools. Not only does the education offered abroad vary greatly by school, but a student may have a variety of options in pursuing his or her ultimate goals of residency training and licensure to practice medicine (Table I). Most of these programs are supported financially or logistically by New York State, and all have very vocal advocates and critics. The diversity of these programs has resulted in great difficulty on the part of licensing or accrediting bodies in evaluating the quality of education provided. This, in turn, has resulted in a morass of regulations and considerable confusion among all concerned, with respect to the role to be played by the US foreign medical graduate (USFMG) in the provision of health care within New York State.

This paper will attempt to assess the current status and future prospects for the United States citizen who chooses to study medicine in a foreign medical school by addressing the following issues: (1) the current need for physicians in New York State; (2) the quality of education received in foreign medical schools; (3) the availability of residency training within the United States for the USFMG; (4) the responses of schools, national organizations, USFMGs and New York State in addressing these issues; and (5) the net effect that these interactions may have on US citizens enrolled in foreign medical schools (USFMS).

PHYSICIAN NEEDS IN NEW YORK STATE

New York State has always been a major resource for training physicians. In 1974 its physician-population ratio made it one of the most physician-dense areas in the world, with the exception of California, the Soviet Union and Israel.[2] Recent statistics provided by the New York State Education Department concerning physician supply within the state through 1990 have demonstrated that there will be more than sufficient physicians to meet needs and, in fact, they confirm the predictions of the Graduate Medical Education National Advisory Committee (GMENAC) concerning a physician surplus.[3]

However, physicians, rather than statistics, provide patient care. It is unfortunate but true that despite the longstanding, favorable ratios of physicians to population in New York State, there have always been and still remain underserved areas. Fortunately, in New York State, similar to prevailing conditions in other states, this maldistribution is slowly being eliminated. Nonetheless, even with these changes, it is anticipated that by 1990 there still may be underserved areas within the state, especially in the inner cities. Therefore, although the numerical need for more physicians in New York State cannot be demonstrated, there certainly is a need to direct those physicians currently in the state to practice in designated areas. To the extent that market conditions finally are prevailing in medicine, the increasing supply of physicians will redress this maldistribution. Unfortunately, the cost-benefit analysis of doing this is far from salutary. Increasing the number of physicians in any area, while being associated with a greater availability of physician services and perhaps a slight decrease in individual fees for service, will be associated with a considerable increase in total expenditures in health care costs—an observation that is often lost on those advocating a continuing increase in physician supply.

THE QUALITY OF EDUCATION IN FOREIGN MEDICAL SCHOOLS

It is extremely difficult, if not impossible, to assess the quality of the education received in many foreign medical schools. There would be little disagreement that those students who are fortunate enough to be accepted with advanced standing into a United States medical school will receive a high quality of training. Similarly, those state residents who enter medical school under a contract program with New York State, albeit in another state or in another country, are thought to receive a comparable education to that received by those attending medical schools within New York State. (Current ongoing contract programs include the University of Vermont, Burlington, VT, Meharry Medical College, Nashville, TN, Morehouse Medical College, Atlanta, GA, and the University of Tel Aviv Sackler School of Medicine, Israel.) Although the quality of Fifth Pathway programs remains somewhat

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Address correspondence to Dr Stimmel, Dean for Academic Affairs, Admissions & Student Affairs, The Mount Sinai Medical Center, One Gustave L. Levy Place, New York, NY 10029.

Dr Stimmel's paper was not presented as part of the symposium. The author was invited to contribute the paper to this issue of the *Journal*.

TABLE I. Reentry of New York State Residents in Foreign Medical Schools to Medical Education in New York State

Acceptance with advanced standing to a United States medical school
Attending a school partially supported by a capitation contract with New York State
Receiving basic clinical training in approved hospitals in New York State
Participation in a Fifth Pathway Program
Completion of all required training on campus at a foreign medical school

controversial in New York State, the establishment of uniform educational requirements prior to admission into these programs, the close supervision of the medical schools that provide support, the high pass rate on the State Licensing Examination of the students that complete these programs and the evaluations of Fifth Pathway students in residency training, suggest that students completing such programs are able to perform in a competent manner.[4,5]

The educational programs in foreign medical schools—especially the newly formed schools that have been developed in the Caribbean, which, together with Mexican schools, represent almost three quarters of all USFMS taking the Educational Commission for Foreign Medical Graduates (ECFMG) examination—are quite difficult to evaluate. The major problem has been the relative lack of clinical facilities in most of these schools, resulting in students attempting to arrange their own clinical preceptorships at hospitals in the United States, predominantly in New York State. As might be expected, the quality of training received by these students in such settings varies greatly.

If one attempts to assess the quality of training by pass rates on the ECFMG examination, a test designed to allow over 90% of the students in United States schools to pass, an average pass rate of 37% is a matter of concern. The pass rate on this examination varies greatly by country, as well as by individual medical school, with pass rates as low as 16% being recorded.[6] The difficulties in providing satisfactory education at many of these schools have been reviewed by the General Accounting Office and need not be repeated.[7] More important than an outside survey, however, are the views of the students. A recent survey of over 400 USFMGs revealed 37% who expressed satisfaction with their clinical training. This proportion varied by country, with 66% of those attending western European schools reporting good to excellent training as compared to 21% of those studying in Mexico.[8]

In reviewing professional activity subsequent to graduating from medical school, problems in obtaining licensure have been noted. McGuinness and Mason[9] found that 34% of USFMGs neither qualified for graduate medical education nor became licensed practitioners. The pass rate on the certifying examination of specialty boards is also lower for USFMGs. The American Board of Internal Medicine has recorded pass rates of 15% to 38% for USFMGs as compared to 39% to 82% for graduates of United States medical schools.[10]

In addition to questions concerning the quality of medical education, a greater concern has been expressed over whether some USFMGs received any medical education at all. Federal and state officials have instituted a widespread investigation to check transcripts and letters of recommendation from a specific school in the Caribbean, following the conviction of an individual who has admitted falsifying credentials of individuals who wished medical degrees.[11] California has acknowledged that 2,500 individuals with suspicious credentials have been identified.[12] The New York State Education Department has recently expressed similar concern and is engaged in an ongoing investigation. Although the precise numbers of students involved are unknown and hopefully small, 1,933 USFMS took the ECFMG examination in the Dominican Republic in 1982, with 322 (16.6%) passing.[6]

In the fall of 1983 the ECFMG invalidated more than 3,000 scores of students taking its examination due to the discovery that widespread dissemination of the examination had occurred at certain testing centers.[13] As a result of the recent problem with some graduates of Dominican Republic schools, the ECFMG has established a stringent set of guidelines to verify the educational experiences of these students.[14]

Situations such as this make it extremely difficult to evaluate the quality of training or competence of students at a number of foreign medical schools. This is not at all to imply that the majority of students studying at these schools are not committed or are not trying to the best of their ability to meet the appropriate educational requirements. It must be emphasized that within the offshore schools, as well as other foreign schools, there are thousands of dedicated students, many of whom will meet all of the necessary requirements and will make meaningful contributions to the provision of health care.

AVAILABILITY OF RESIDENCY TRAINING

Each year, despite the problems that may exist in the quality of education in some foreign medical schools, considerable numbers of USFMS graduate and meet the standards for entering residency training in this country. These numbers have increased greatly over the past several years, resulting in an unprecedented number of USFMGs applying for residency training. Although the number of Fifth Pathway graduates has actually decreased by 10% between 1981 and 1984, from 456 to 411, the number of USFMGs has increased from 785 to 2,931 (273%) during this period, with the number of alien foreign medical graduates (AFMGs) increasing by more than 300%.[15] Even these data, however, are incomplete, as a number of USFMGs may choose not to enter the matching program, opting to apply to institutions not in the match or waiting to file applications for unfilled positions once the matching results have been announced.

Since 1982 the increase in USFMGs and AFMGs has resulted in more applicants applying to the National Resident Matching Program (NRMP) than available positions. In the 1984 match, despite the small increase in the number of positions offered for first-year, post-graduate training, the ratio of positions per enrolled applicant was 0.6. Not unexpectedly, this has resulted in decreasing match rates for the USFMGs. In 1984, while graduates of United States medical schools experienced an 8% non-match rate, 22% of Fifth Pathway students and 56% of USFMGs remained

TABLE II. Students Not Matching in the National Resident Matching Program

	1981		1982		1984		% Increase 1981–1984*
	No.	(%)	No.	(%)	No.	(%)	
United States senior students	981	(7)	1121	(8)	1153	(8)	17
Fifth Pathway students	60	(17)	107	(25)	76	(22)	27
United States foreign medical graduates	174	(32)	407	(43)	943	(56)	442
Alien foreign medical graduates	617	(55)	1641	(69)	3290	(78)	433

* In number of unmatched students

unmatched (Table II).[16] If one adds to this the pool of unmatched physicians reentering the match osteopaths, Canadian students and the AFMGs, a total of 5,940 unmatched applicants existed for 2,399 positions. Since it can be assumed that the 1,153 United States students who had just completed medical school would have priority with respect to matching, the 4,787 physicians remaining unmatched would be competing for only 1,246 positions. This ratio is far from optimal. Furthermore, there are a considerable number of USFMGs who choose not to participate in the match. A recent report noted that of a randomly selected pool of over 400 USFMGs, only 47% participated in the NRMP.[8] This year, as in the past two years, there will be many USFMGs who have met the requirements for graduate education but are unable to obtain a residency position in any field.

The fate of these physicians remains unclear. Some will try to reenter the match again the following year, but the likelihood of their success is no greater. Although a different career may be pursued, a more likely possibility will be an attempt to enter practice in one of the few remaining states that do not require residency training as a prerequisite for licensure. It appears, therefore, that not only may there be an excess of licensed physicians, but in addition, there will be a continuing increase in the numbers of physicians, mainly those trained in foreign medical schools, who will have spent considerable time, effort and resources to obtain a medical degree but are unable to practice medicine.

RESPONSES OF NATIONAL AGENCIES

The responses of the various agencies involved with accrediting medical schools have been conflicting. The Association of American Medical Colleges has long favored the transfer of USFMS with advanced standing to United States medical schools but has consistently refused to endorse Fifth Pathway programs. This policy has given little support to those students that graduate from foreign medical schools. The American Medical Association has always supported Fifth Pathway programs and provides low interest loans to USFMS. The association has expressed concern over the increasing numbers of USFMS and the quality of education provided by these schools.[17] The Liaison Committee on Medical Education (LCME), which approves all medical schools in the United States, has maintained steadfastly that it is not within their jurisdiction to accredit schools outside of the United States. It was reported recently that the ability of the LCME to accredit schools within the United States is being challenged. The LCME is allegedly being taken to court for refusing to accredit a school in Puerto Rico, suggesting that even approving schools under their own aegis is not an easy task.[18]

By nature of the accrediting process, the major role of assuring minimal competence before the stage of residency training has fallen to the ECFMG. Several years ago, in an attempt to initiate a common standard of testing, the ECFMG developed the Visa Qualifying Examination (VQE) for alien foreign graduates who wished to undergo graduate training in this country. This examination, standardized to the National Board Examinations, resulted in a pass rate of approximately 27%, mainly due to the introduction of a basic science section. USFMGs, however, were still permitted to sit for the ECFMG examination. In an attempt to provide uniform standards for all, the ECFMG, commencing in July 1985, will replace both the VQE and the ECFMG examination with a single two-day test—the Foreign Medical Graduate Examination in the Medical Sciences.[19] This examination will be a standardized equivalent to Parts I and II of the National Board Examinations.

The Federation of State Medical Boards, long concerned with their state licensing examination, is meeting with national medical groups to prepare for introducing the FLEX I and FLEX II examinations. In June 1985, FLEX I must be passed before a graduate can proceed to the second year of residency training; FLEX II must be passed to qualify for unrestricted medical licensure.[20] In addition, work is currently underway, via a consortium of organizations, to develop a uniform examination to test clinical competency in addition to basic science and clinical knowledge.

RESPONSES OF THE STATES

The responses of individual states to the perceived physician excess, most especially towards USFMGs, has been confusing to say the least. For example, the Board of Quality Medical Assurance in California has developed "uniform standards" of quality medical education that ultimately may or may not exclude USFMGs but has eliminated those graduates of United States medical schools who have attended either accelerated MD/PhD programs or the Sophie Davis Biomedical Program of The City College of The City University of New York.[21] Exclusion of this latter group of students is particularly puzzling as they are not only among the more competent students, but they actually received MD degrees from the LCME approved schools where they spent their last two years of medical training.

New York State has a continuing interest in USFMS. This is related not only to the general concern with health care in the state, but also to the large numbers of New York State residents studying medicine at these schools who return to hospitals within the state for undergraduate clinical training, Fifth Pathway programs and residency training. Although it is hard to determine the numbers of students involved, New York State currently trains 50% of all students participating in Fifth Pathway programs.

At present, New York State's response is inconsistent at best. The two major state agencies that address this issue, the Department of Health and the State Education Department, seem to be moving toward opposing objectives.[22] The State Education Department, headed by the Board of Regents, appears to be encouraging the entry of USFMS and has developed a process of approval of offshore medical schools that makes it easier for students from these schools to take their clinical training at hospitals in New York State.[15] Those students from unapproved schools, while still able to take training within the state, are not able to do so for more than 12 weeks during a two-year period.

The Department of Health, however, has committed itself to limiting the numbers of USFMS that train in the state. The department has called for the elimination of state support for capitation of Fifth Pathway programs and advanced transfer programs as well as an end to contract programs between New York State and out-of-state medical schools.

Whereas the elimination of the Fifth Pathway and contract programs allows other USFMS to take their clinical training in this state, it will cause those USFMS able to receive medical education of proven quality to transfer to other foreign medical schools—where the quality of education is extremely variable—without actually decreasing the numbers of USFMGs. In addition, the department is on record as being ready to implement an old provision of the State Education Law (Section 6512) which prohibits students from unapproved foreign medical schools from taking clinical training in any hospital in New York State. Violation of this statute is a Class E Felony and, as noted in a recent Department of Health memorandum, "persons that aid and abet the unauthorized practice of medicine may also be in violation."[23,24]

The net result of these policies is a series of complex regulations that schools must follow in order to allow students in any foreign medical school to take clinical training in hospitals within New York State. These requirements vary with specific foreign schools as well as with the student's date of matriculation. Making hospitals in New York State responsible for assuring that the student meets all state requirements and has not taken electives at any other hospital within the state is far from reasonable. These regulations may well serve as a disincentive for medical schools and hospitals in the state to take students from foreign medical schools for elective training.

Response of United States Medical Schools

The medical schools in New York State have always tried to be responsive to residents that attend schools outside of the United States, without compromising either the quality of education offered their own students or their standards of admission. As noted above, public medical schools admit more than 90% state residents, and the private schools have tried to meet a 70% state resident requirement. This has not been easy for some private schools. Indeed, due to the large number of New York State residents that apply to medical school, the number of New York State residents able to attend medical school in this country would probably decrease, should the private schools become too restrictive, and private schools in other states respond in kind.

Schools in New York State, on a space-available basis, continue to accept students from foreign medical schools with advanced standing, although the numbers of these students nationwide have decreased from 858 in 1978 to 354 in 1982. Nonetheless, medical schools in New York accept a disproportionate number of this nationwide pool. Seven of the 12 medical schools in the state have sponsored Fifth Pathway programs. These programs, responsible for training 50% of all Fifth Pathway students in the country, have always been able to accommodate any New York State resident who meets the basic admissions requirements. It is unfortunate that, due to continuing state pressure, the State University of New York has announced its intentions to discontinue such programs in the near future.

Finally, although not in complete agreement with all aspects of the Regents' policy of approving foreign medical schools, faculty have served, at the request of the State Education Department, as members of site visit teams that evaluate the schools.

Response of US Foreign Medical Students

The USFMS have been far from quiet during this period of turmoil. As the number of degree-granting, four-year medical schools in the Caribbean has grown, the enrollment of students in Fifth Pathway programs has started to decline. This is probably related to the ability of students in Caribbean schools to obtain a degree after four years, immediately entering residency training after passing the ECFMG examination, without the extra year of clinical training. Although the attempts by students to avoid both the cost and time involved in this extra year are understandable, it is unfortunate that these programs, which have been shown to provide additional clinical skills, are undergoing attrition.

Enrollment patterns of USFMGs also suggest that the graduates are becoming more aware of the quality of education received at some schools, with those that offer a better education becoming more competitive. As information concerning pass rates on the ECFMG examination become available, students are better able to assess the merits of attending a particular school. For example, it is alleged that one recently established offshore school has had to close due to its inability to attract students.[22]

USFMGs appear to be enthusiastic about remaining in New York State subsequent to completion of residency training. Whether this is due to their originally being state residents or their exposure to the practice of medicine in the state during clinical clerkships or residency training is unclear. Nonetheless, a recent survey has shown New York to rank first in preference for practice location (20%), followed by California (14%) and New Jersey (12%).[8] The attempts by these states to restrict entry of USFMGs are not favorably received.

The last resort in protesting any bureaucratic process is litigation, and in this area the students and their parents have been very effective. One organization that claims to represent 15,000 students has been a potent political lobbying force.[25] This organization, as well as others, has retained counsel, and suits have been initiated in a number of states that have denied licensure to USFMGs. Perhaps as these cases proceed through the courts, the ability of the USFMG to provide medical care in this country will become more clearly defined.

CONCLUSIONS

In summary, the role of the USFMG in the provision of health care is increasing. The numbers of USFMS have been growing and, at present, show little sign of diminishing. Whether there is a "physician glut" remains controversial; however, it is incontestable that each year there will be a number of USFMGs who have met the appropriate standards yet are unable to obtain residency training positions and, therefore, to practice medicine. The response of New York State to this problem has, unfortunately, not been entirely consistent. This has resulted in confusion on the part of the students and the medical schools in the state. In addition, New York State's longstanding tradition of promoting excellence in international medicine by providing clinical experience and residency training to alien physicians may be in jeopardy. It is likely that the first programs dealing with USFMS to be eliminated will be those that provide the best education. This will decrease the overall preparation of USFMS, but will not affect the total number of USFMGs entering the state.

On the positive side, the development of a single standard for licensure—regardless of medical school attended, due to the efforts of the ECFMG, the National Board of Medical Examiners and the Federation of State Medical Boards, is laudable. Any "paper and pen" examination, however, is insufficient to test clinical competence. Continuing interest in the development of a standardized and equitable method to assess clinical competence prior to residency training is encouraging. The administration of such testing procedures need not be restricted to graduates of foreign medical schools. Such tests would be of equal value to assure a minimum level of competence in students graduating from United States schools. The development of such standards, equitably applied, will ultimately benefit both physicians and the public.

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The *New York State Journal of Medicine* welcomes research papers and original essays on the practice of medicine, medical education, public health, the history of medicine, medicolegal matters, legislation, ethics, the mass media and socioeconomic issues in health care.

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Sample references:

1. Kepes ER, Thomas P, Vemulapalli K: Methadone and intravenous morphine requirements. *NY State J Med* 1983; 83: 925–927.
2. McGuigan JE. Peptic ulcer. In: Petersdorf RG, Adams RD, Braunwald E, Isselbacher KJ, Martin JB, Wilson JD, eds. *Harrison's Principles of Internal Medicine*. New York, McGraw-Hill, 1983, pp 1697–1712.

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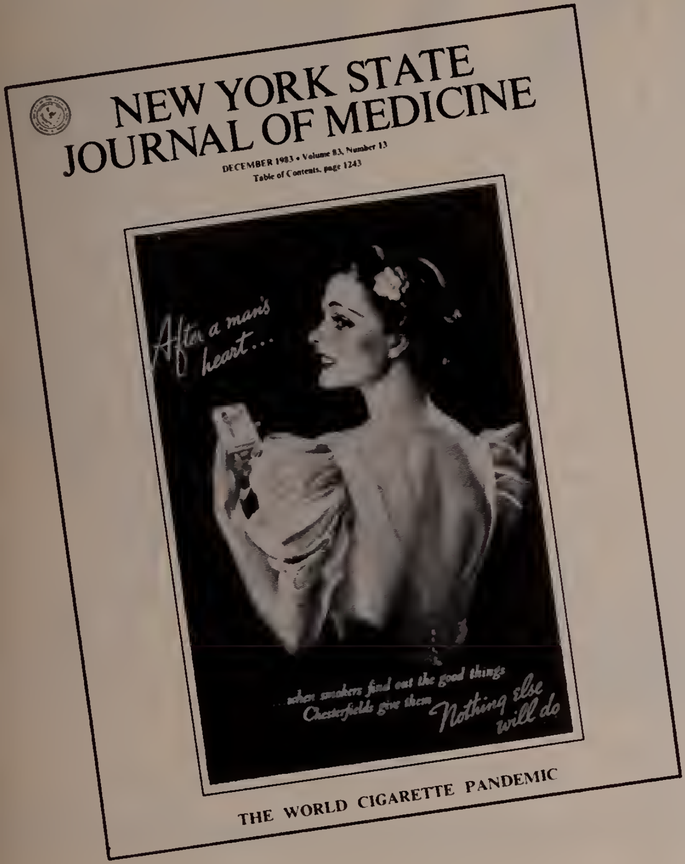

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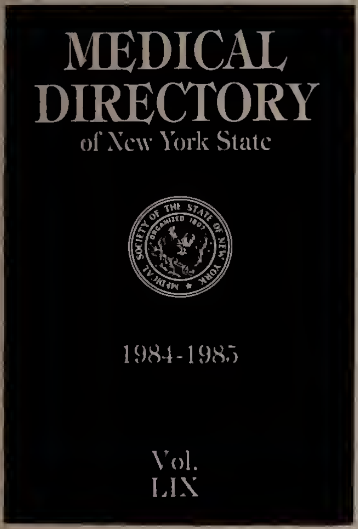

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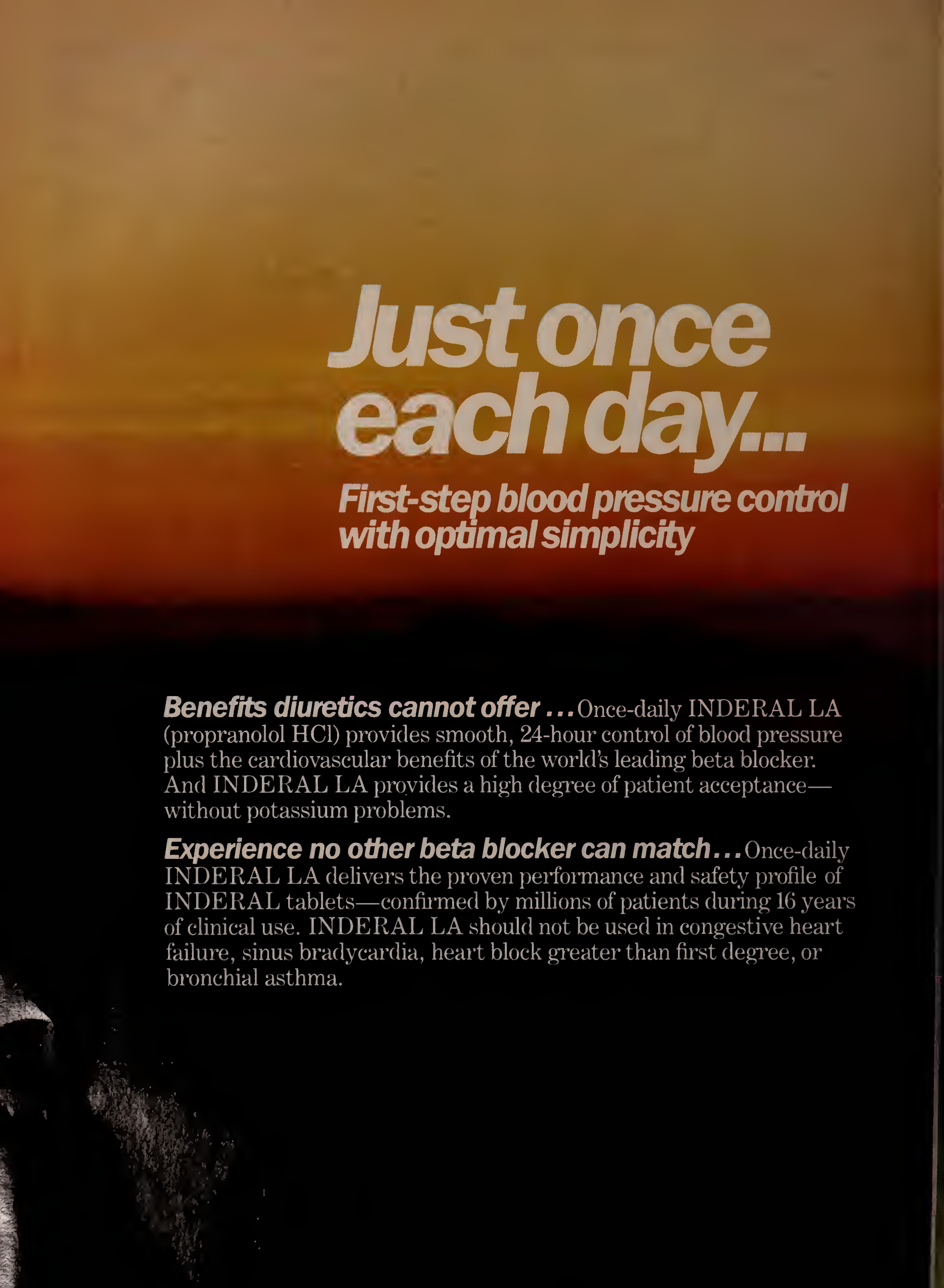

Just once each day...

First-step blood pressure control with optimal simplicity

Benefits diuretics cannot offer . . . Once-daily INDERAL LA (propranolol HCl) provides smooth, 24-hour control of blood pressure plus the cardiovascular benefits of the world's leading beta blocker. And INDERAL LA provides a high degree of patient acceptance—without potassium problems.

Experience no other beta blocker can match . . . Once-daily INDERAL LA delivers the proven performance and safety profile of INDERAL tablets—confirmed by millions of patients during 16 years of clinical use. INDERAL LA should not be used in congestive heart failure, sinus bradycardia, heart block greater than first degree, or bronchial asthma.

Start with 80 mg once daily... Dosage may be increased to 120 mg or 160 mg once daily as needed to achieve additional control. Please see next page for further details and brief summary of prescribing information.

ONCE-DAILY

INDERAL LA

(PROPRANOLOL HCl) LONG-ACTING CAPSULES

Just once each day for initial therapy in hypertension.

The appearance of INDERAL LA capsules is a registered trademark of Ayerst [illegible]

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Just once each day for initial therapy in HYPERTENSION.

ONCE-DAILY

INDERAL® LA

(PROPRANOLOL HCl) LONG ACTING CAPSULES

Just once each day...

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)*
INDERAL® LA brand of propranolol hydrochloride **(Long Acting Capsules)**

DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.

CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and [illegible]ewhat variable. INDERAL has been shown to cause a small increase in serum potassi[illegible] concentration when use[illegible] the treatment of hypertensive patients

In angina pectoris, propranolol generally reduces th[illegible]n re[illegible] any given level of effort by blocking the catecholamine-[illegible] inc[illegible] the h[illegible] rate, systolic blood pressure, and the velocity and extent of [illegible]dial [illegible]nolol may increase oxygen requirements by increasing left [illegible]lar f[illegible] length, [illegible]stolic pressure and systolic ejection period The net phy[illegible]e is usually advantageous and is manifested duri[illegible]rcis[illegible]nd increased work capacity

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-[illegible] or anesthetic-like membrane action which affects th[illegible]c a[illegible]nti[illegible]ig[illegible]cance of the membrane action in the treatment of [illegible]ythm[illegible]cer[illegible]

The mechanism of the antimigraine effect of pr[illegible]lished. B[illegible]-adrenergic receptors have been demonstrated in [illegible]pial vess[illegible] of the [illegible]

Beta receptor blockade can be useful in con[illegible]ns in [illegible] bec[illegible]path[illegible]r functional changes, sympathetic activity is detri[illegible]so situations in which sympathetic stimulation is vital. F[illegible] exampl[illegible] in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension, it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first degree block; 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL

WARNINGS. CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

> IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)— PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors

MAJOR SURGERY The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers

DIABETES AND HYPOGLYCEMIA Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker In one case this resulted after an initial dose of 5 mg propranolol

PRECAUTIONS. *General.* Propranolol should be used with caution in patients with impaired hepatic or renal function INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure Patients should be told that INDERAL may interfere with the glaucoma screening test Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in [illegible]rats [illegible] mic[illegible] empl[illegible]oses [illegible] 150 mg/kg/day, there was no evidence of significant [illegible]lated tumorigenic effects at any of the dosage levels [illegible]duc[illegible]dies [illegible]rials [illegible] not show any impairment of fertility that was attrib[illegible] to th[illegible]

[illegible]ncy. [illegible]ncy Cat[illegible]ry C. INDERAL has been shown to be embryotoxic in an[illegible]ies a[illegible]er than the maximum recommended human dose There are n[illegible]equ[illegible]d w[illegible]olled studies in pregnant women. INDERAL should be used during p[illegible]gnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mot[illegible]s INDERAL is excreted in human milk Caution should be exercised when [illegible]DERAL [illegible]dm[illegible]ste[illegible] a [illegible]rsing w[illegible]an.

Pe[illegible]ric [illegible]ety a[illegible]ctive[illegible]ss in children have not been established

[illegible]VE[illegible]SE R[illegible]ACTIONS [illegible] ad[illegible]se effects have been mild and transient and have [illegible]rely [illegible]quired [illegible] of [illegible]

C[illegible]diovas[illegible] brady[illegible]dia [illegible]gestive heart failure, intensification of AV block, hypo-[illegible]nsio[illegible] thr[illegible]urpura, arterial insufficiency, usually of the [illegible]aynaud type.

Central Nervous System [illegible]headedness, mental depression manifested by insomnia, lassitude, weakness, fatigue, [illegible]eversible mental depression progressing to catatonia, visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics

Gastrointestinal nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic. pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Auto-Immune. In extremely rare instances, systemic lupus erythematosus has been reported

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved The usual maintenance dosage is 120 to 160 mg once daily In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks

ANGINA PECTORIS—*Dosage must be individualized* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS)

MIGRAINE—*Dosage must be individualized* The initial oral dose is 80 mg INDERAL LA once daily The usual effective dose range is 160-240 mg once daily The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued It may be advisable to withdraw the drug gradually over a period of several weeks

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use

*The appearance of INDERAL LA capsules is a registered trademark of Ayerst Laboratories

8950/284

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AYERST LABORATORIES
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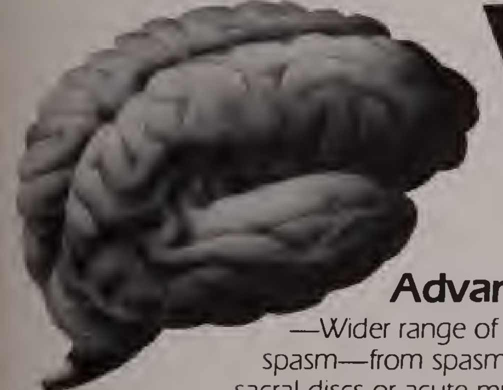
THE SPASM/PAIN/SPASM CYCLE

In skeletal muscle spasm due to local pathology, responsive to the distinct actions of



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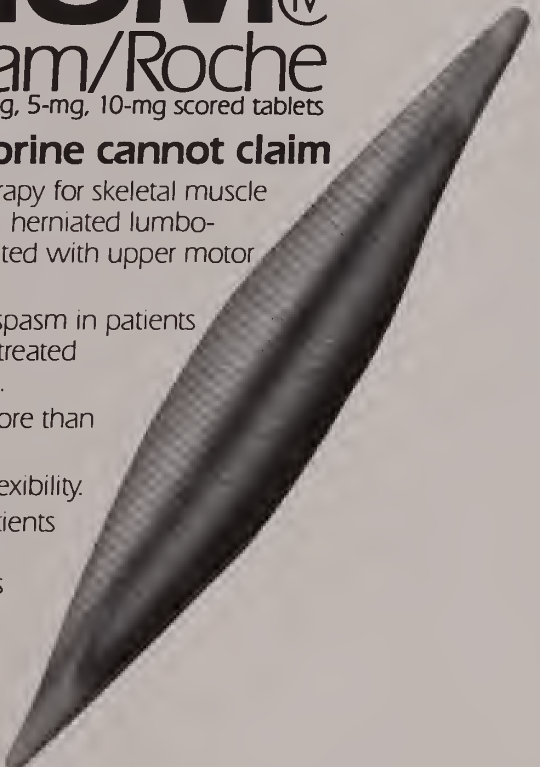


Advantages cyclobenzaprine cannot claim

—Wider range of indications as adjunctive therapy for skeletal muscle spasm—from spasm due to local pathology (*e.g.*, herniated lumbosacral discs or acute muscle strain) to spasm associated with upper motor neuron disorders (*e.g.*, cerebral palsy and paraplegia).

—May be used adjunctively for relieving skeletal muscle spasm in patients with hyperthyroidism, cardiac patients and patients being treated with anticholinergics or guanethidine-type antihypertensives.

—Can be administered to patients less than 15 years and more than 6 months of age.

—Scored tablets in three strengths provide greater dosage flexibility.

Since drowsiness, fatigue and ataxia sometimes occur, patients should be cautioned against driving or operating hazardous machinery and should also be advised against simultaneous ingestion of alcohol.

References: 1. Rankin EA: *Contin Educ 3*(1):46-50, Jan 1975. **2.** When muscle spasm hobbles your patient. *Patient Care 8*(11):20-37, Jun 1, 1974.

Valium® (diazepam/Roche) Ⓘⓥ
Before prescribing, please consult complete product information, a summary of which follows:
Indications: Management of anxiety disorders, or short-term relief of symptoms of anxiety Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic Symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal, adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not as sole therapy)
The effectiveness of Valium in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies The physician should periodically reassess the usefulness of the drug for the individual patient
Contraindicated: Known hypersensitivity to the drug Children under 6 months of age Acute narrow angle glaucoma, may be used in patients with open angle glaucoma who are receiving appropriate therapy
Warnings: Not of value in psychotic patients Caution against hazardous occupations requiring complete mental alertness When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication, abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures Advise against simultaneous ingestion of alcohol and other CNS depressants Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use, generally at higher therapeutic levels, for at least several months After extended therapy, gradually taper dosage Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence

***Usage in Pregnancy*: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

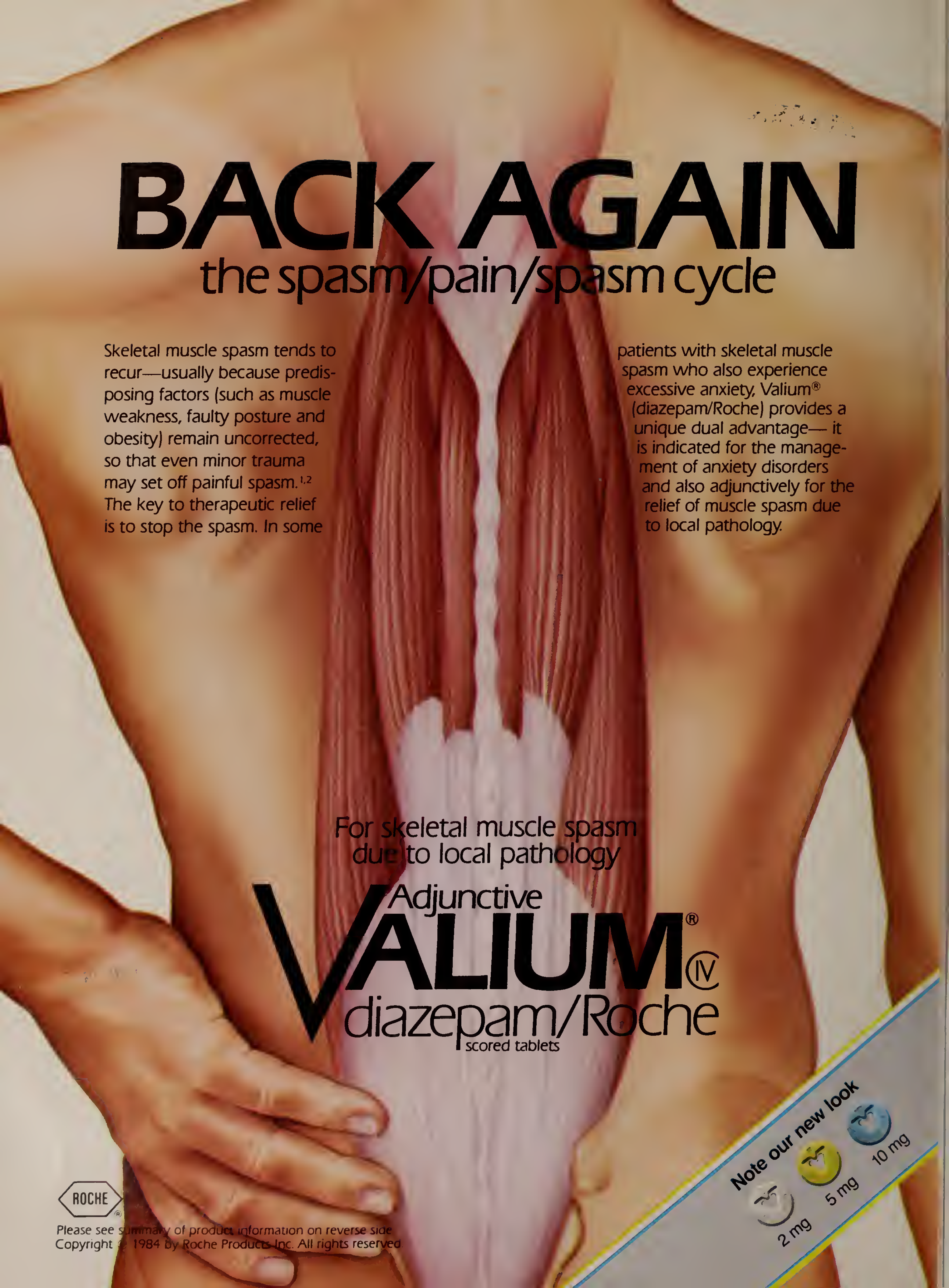
Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed, drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies Observe usual precautions in impaired renal or hepatic function Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation
The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration The clinical significance of this is unclear
Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported, should these occur, discontinue drug Isolated reports of neutropenia, jaundice, periodic blood counts and liver function tests advisable during long-term therapy
Dosage: Individualize for maximum beneficial effect *Adults* Anxiety disorders, symptoms of anxiety, 2 to 10 mg b.i d to q i.d , alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i d or q i.d as needed, adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d or q.i.d , adjunctively in convulsive disorders, 2 to 10 mg b i.d to q.i.d. *Geriatric or debilitated patients* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated (See Precautions.) *Children* 1 to 2½ mg t.i.d or q.i.d. initially, increasing as needed and tolerated (not for use under 6 months).
How Supplied: For oral administration, round, scored tablets with a cut out "V" design—2 mg, white, 5 mg, yellow, 10 mg, blue— bottles of 100 and 500, Prescription Paks of 50, available in trays of 10 Tel-E-Dose® packages of 100, available in boxes of 4 reverse-numbered cards of 25, and in boxes containing 10 strips of 10

Imprint on tablets
2 mg—2 VALIUM® (front)
ROCHE (scored side)

5 mg—5 VALIUM® (front)
ROCHE (scored side)

10 mg—10 VALIUM® (front)
ROCHE (scored side)

ROCHE®
ROCHE PRODUCTS INC
Manati, Puerto Rico 00701



BACK AGAIN
the spasm/pain/spasm cycle

Skeletal muscle spasm tends to recur—usually because predisposing factors (such as muscle weakness, faulty posture and obesity) remain uncorrected, so that even minor trauma may set off painful spasm.[1,2] The key to therapeutic relief is to stop the spasm. In some patients with skeletal muscle spasm who also experience excessive anxiety, Valium® (diazepam/Roche) provides a unique dual advantage— it is indicated for the management of anxiety disorders and also adjunctively for the relief of muscle spasm due to local pathology.

For skeletal muscle spasm due to local pathology

Adjunctive
VALIUM® ⓘⓥ
diazepam/Roche
scored tablets

ROCHE

Please see summary of product information on reverse side

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STACKS

NEW YORK STATE JOURNAL OF MEDICINE

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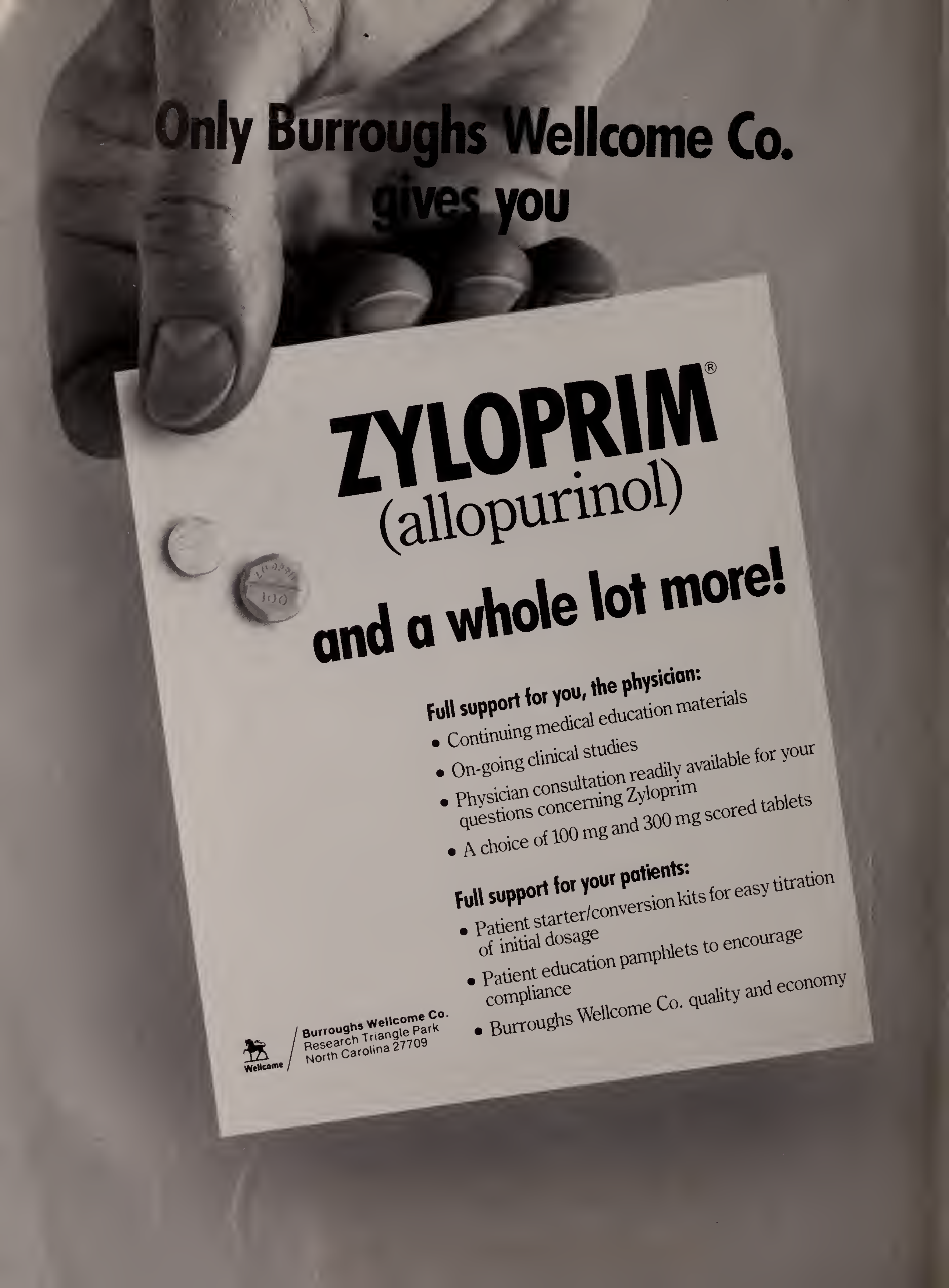

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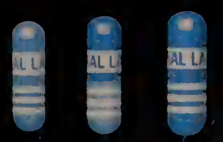

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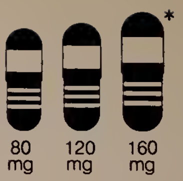

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)*
INDERAL® LA brand of propranolol hydrochloride **(Long Acting Capsules)**
DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.
CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and [illegible]ewhat variable. INDERAL has been shown to cause a small increase in serum potassi[illegible] concentration when use[illegible] the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces th[illegible] re[illegible] any given level of effort by blocking the catecholamine-[illegible] inc[illegible] the h[illegible] rate, systolic blood pressure, and the velocity and extent of [illegible]dial [illegible]nolol may increase oxygen requirements by increasing left [illegible]lar f[illegible] length, [illegible]stolic pressure and systolic ejection period. The net phy[illegible]e is usually advantageous and is manifested duri[illegible]rcis[illegible]nd increased work capacity.

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-[illegible] or anesthetic-like membrane action which affects th[illegible]c a[illegible]nifi[illegible]cance of the membrane action in the treatment of [illegible]ythm[illegible]ce[illegible]

The mechanism of the antimigraine effect of pr[illegible]lished. Beta-adrenergic receptors have been demonstrated in [illegible] pial ves[illegible] of the [illegible]

Beta receptor blockade can be useful in con[illegible]ns in [illegible] bec[illegible] path[illegible]r functional changes, sympathetic activity is detrim[illegible]so situations in which sympathetic stimulation is vital. F[illegible] exampl[illegible] in patients w[illegible] severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first degree block; 3) bronchial asthma; 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS. CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

> IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. *General:* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in [illegible]ats [illegible] emplo[illegible] dose[illegible] 150 mg/kg/day, there was no evidence of significant [illegible]lated tumorigenic effects at any of the dosage levels [illegible] duc[illegible]dies [illegible]mals [illegible] not show any impairment of fertility that was attrib[illegible] to th[illegible]

[illegible]ncy: [illegible]ncy Cat[illegible]ry C. INDERAL has been shown to be embryotoxic in [illegible]ies a[illegible]er than the maximum recommended human dose. Th[illegible] are n[illegible] adequ[illegible] w[illegible]trolled studies in pregnant women. INDERAL should be used during p[illegible]gnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mot[illegible]s: INDERAL is excreted in human milk. Caution should be exercised when [illegible]DERAL [illegible] a [illegible]sing w[illegible]man.

Pe[illegible]ric [illegible]ety a[illegible]ctive[illegible]ss in children have not been established.

[illegible]VE[illegible]SE R[illegible]CTIONS [illegible] adv[illegible]se effects have been mild and transient and have [illegible]rely [illegible]quired [illegible] of [illegible]y.

C[illegible]diovas[illegible] [illegible]brady[illegible]dia[illegible]gestive heart failure; intensification of AV block; hypo[illegible]nsion[illegible] thr[illegible]urpura; arterial insufficiency, usually of the [illegible]aynaud type.

Central Nervous System: [illegible]headedness, mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized.* The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily.

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

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AROUND THE STATE

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Sept 18. **A Controlled Study of Attitudinal Changes in Response to Liaison Psychiatry Teaching.** Lenox Hill Hospital. Info: Mrs V Matthes, 542 Baldwin Ave, Baldwin, NY 11510. Tel: (516) 379-1787.

Sept 20. **Symposium on Myocardial Infarction Care.** 2 Cat 1 credits. New York City. Info: The New York Cardiological Society, Inc, 84 Grove St, Ste 2, New York, NY 10014. Tel: (212) 924-5346.

Sept 22. **Workshop on Genetics & Craniofacial Anomalies.** 6½ Cat 1 credits. Info: New York University, Division of Human Genetics MSB-136, 550 First Ave, New York, NY 10016. Tel: (212) 340-5746.

Sept 22–23. **Acute Cardiopulmonary Disease.** 20 Cat 1 credits. New York City. Info: Mary J. Ryals, Ryals & Associates, PO Box 61203, DFW Airport, TX 75261. Tel: (214) 659-9590.

Sept 23. **Clinical Application of the New Genetics.** New York City. Info: Leona J. Schumer, March of Dimes, 622 Third Ave, New York, NY 10017. Tel: (212) 922-1460.

Sept 26–30. **A Clinical and Histopathologic Overview of Obstetrics and Gynecology.** New York City. Info: James L. Breen, MD, Chairman, Dept of Obstetrics & Gynecology, Saint Barnabas Medical Center, Livingston, NJ 07039.

BRONX

Sept 6. **Metabolic Bone Disease.** 2 Cat 1 credits. *Sept 13.* **Multiple Sclerosis.** 2

continued on p. 14A

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White Plains	Oct 9, 1984	White Plains Hotel • S. Broadway & Lyon Pl.
Saddle Brook (New Jersey)	Oct 10, 1984	Treadway Inn at Saddle Brook • 50 Kenney Pl.
Long Island/ Smithtown	Oct 11, 1984	Sheraton Smithtown • 110 Vanderbilt Motor Parkway
New York City	Oct 12, 1984	Plaza Hotel • Fifth Avenue at 59th
Schenectady	Oct 25, 1984	Ramada Inn/Convention Center • 450 Knott Ter.
Utica	Oct 26, 1984	Sheraton Inn • 200 Gennessee St.

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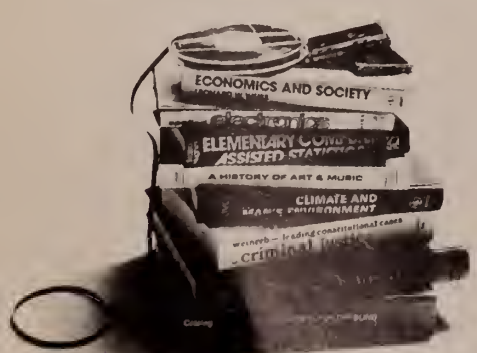

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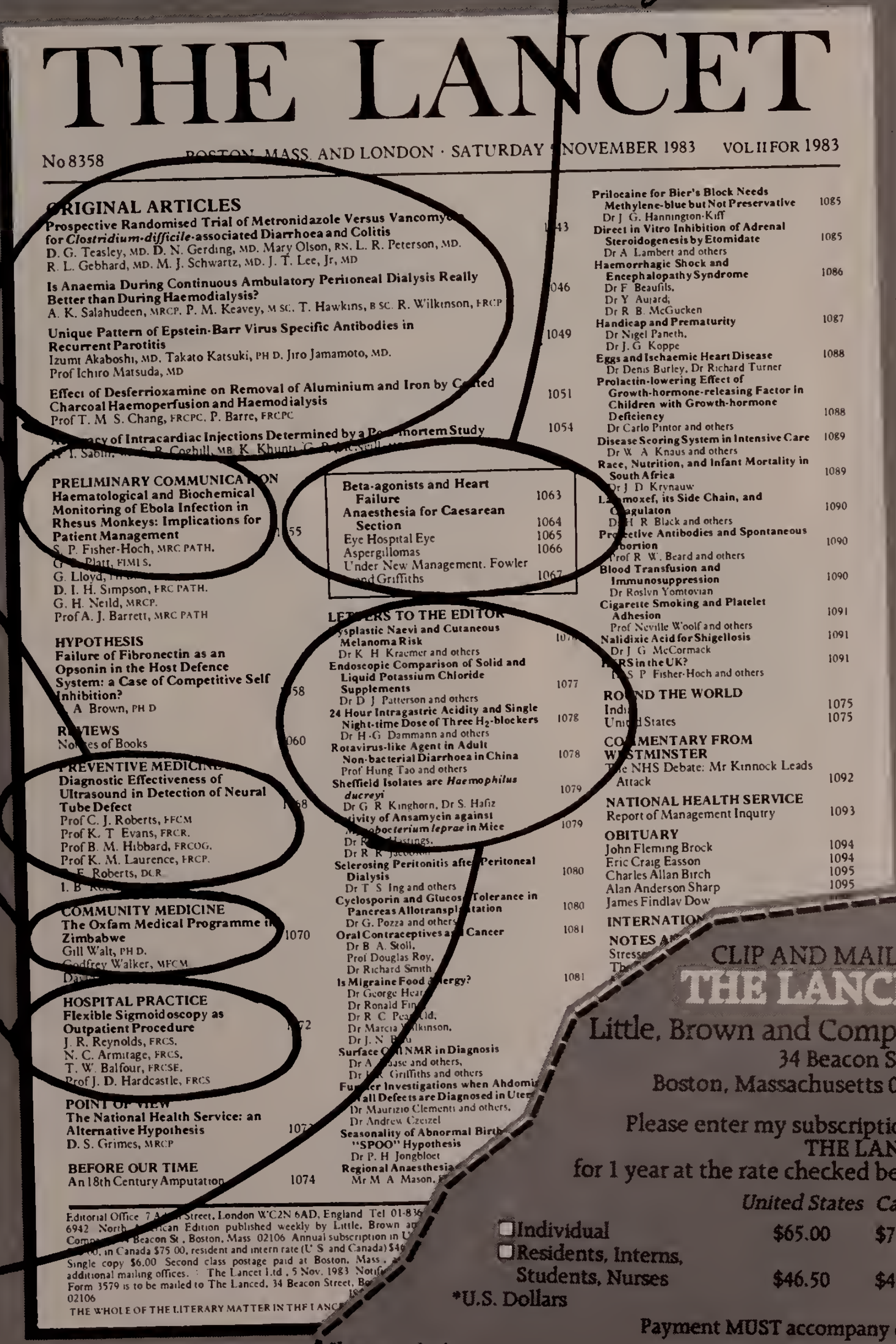

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Editorial Office 7 Adam Street, London WC2N 6AD, England Tel 01-836 6942 North American Edition published weekly by Little, Brown and Company, 34 Beacon St., Boston, Mass 02106 Annual subscription in U ... 00, in Canada $75 00, resident and intern rate (U S and Canada) $46 Single copy $6.00 Second class postage paid at Boston, Mass., additional mailing offices. © The Lancet Ltd., 5 Nov. 1983 Notif Form 3579 is to be mailed to The Lanced, 34 Beacon Street, Bo 02106
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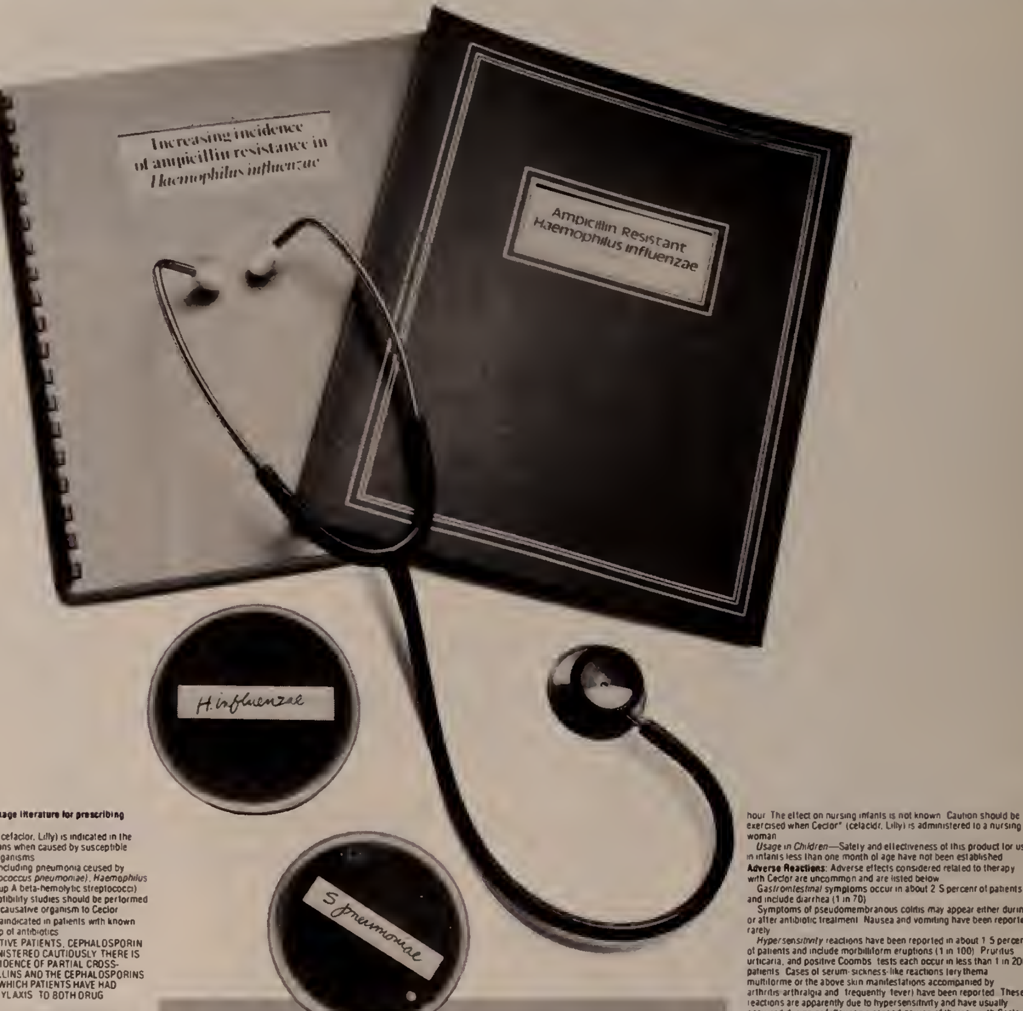
An added complication... in the treatment of bacterial bronchitis*



Increasing incidence of ampicillin resistance in Haemophilus influenzae
Ampicillin Resistant Haemophilus influenzae
H influenzae
S pneumoniae

Some ampicillin-resistant strains of Haemophilus influenzae—a recognized complication of bacterial bronchitis*—are sensitive to treatment with Ceclor.[1-6]

In clinical trials, patients with bacterial bronchitis due to susceptible strains of Streptococcus pneumoniae, H. influenzae, S. pyogenes (group A beta-hemolytic streptococci), or multiple organisms achieved a satisfactory clinical response with Ceclor.[7]

Ceclor®
cefaclor

Pulvules®, 250 and 500 mg

Brief Summary. Consult the package literature for prescribing information.

Indications and Usage: Ceclor® (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae (Diplococcus pneumoniae)*, *Haemophilus influenzae*, and *S. pyogenes* (group A beta-hemolytic streptococci)

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor.

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES.

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics. Such colitis may range in severity from mild to life-threatening.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis.

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation. When the colitis does not improve after the drug has been discontinued, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be ruled out.

Precautions: *General Precautions*—If an allergic reaction to Ceclor occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids.

Prolonged use of Ceclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug.

Ceclor should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly).

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Usage in Pregnancy—Pregnancy Category B—Reproduction studies have been performed in mice and rats at doses up to 12 times the human dose and in ferrets given three times the maximum human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Ceclor. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers—Small amounts of Ceclor have been detected in mother's milk following administration of single 500-mg doses. Average levels were 0.18, 0.20, 0.21, and 0.16 mcg/ml at two, three, four, and five hours respectively. Trace amounts were detected at one hour. The effect on nursing infants is not known. Caution should be exercised when Ceclor® (cefaclor, Lilly) is administered to a nursing woman.

Usage in Children—Safety and effectiveness of this product for use in infants less than one month of age have not been established.

Adverse Reactions: Adverse effects considered related to therapy with Ceclor are uncommon and are listed below.

Gastrointestinal symptoms occur in about 2.5 percent of patients and include diarrhea (1 in 70).

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely.

Hypersensitivity reactions have been reported in about 1.5 percent of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients. Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever) have been reported. These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Ceclor. Such reactions have been reported more frequently in children than in adults. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain—Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic—Slight elevations of SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic—Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal—Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200).

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*Many authorities attribute acute infectious exacerbation of chronic bronchitis to either *S. pneumoniae* or *H. influenzae*.[8]

Note: Ceclor is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

References

1. Antimicrob Agents Chemother *8*:91, 1975
2. Antimicrob Agents Chemother *11*:470, 1977
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5. Current Chemotherapy (edited by W. Siegenthaler and R. Luthy), II:880. Washington, D.C.: American Society for Microbiology, 1978
6. Antimicrob Agents Chemother *13*:861, 1978
7. Data on file, Eli Lilly and Company
8. Principles and Practice of Infectious Diseases (edited by G. L. Mandell, R. G. Douglas, Jr., and J. E. Bennett), p. 487. New York, John Wiley & Sons, 1979

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BALANCED CALCIUM CHANNEL BLOCKADE!

CARDIZEM®
(diltiazem HCl)
balances potent coronary vasodilation with a low incidence of side effects

Low incidence of side effects
CARDIZEM® (diltiazem HCl) produces an incidence of adverse reactions not greater than that reported with placebo therapy, thus contributing to the patient's sense of well-being.

Reduces angina attack frequency*
42% to 46% decrease reported in multicenter study.[1]

Increases exercise tolerance*
In Bruce exercise test,[2] control patients averaged 8.0 minutes to onset of pain; Cardizem patients averaged 9.8 minutes ($P<.005$).

CARDIZEM®
(diltiazem HCl)

THE BALANCED CALCIUM CHANNEL BLOCKER

Please see full prescribing information on following page.

2/84

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*Cardizem is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

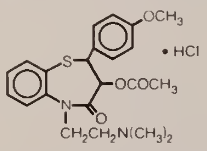
References:
1. Strauss WE, McIntyre KM, Parisi AF, et al: Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris: Report of a cooperative clinical trial. Am J Cardiol 49:560-566, 1982.
2. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. Chest 78 (July suppl):234-238, 1980.

PROFESSIONAL USE INFORMATION

cardizem®
(diltiazem HCl)
30 mg and 60 mg tablets

DESCRIPTION

CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+)-cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem hydrochloride for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina. CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIONS and ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS).

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%), AV block (1.1%). In addition, the following events were reported infrequently (less than 1%) with the order of presentation corresponding to the relative frequency of occurrence.

Cardiovascular:	Flushing, arrhythmia, hypotension, bradycardia, palpitations, congestive heart failure, syncope.
Nervous System:	Paresthesia, nervousness, somnolence, tremor, insomnia, hallucinations, and amnesia.
Gastrointestinal:	Constipation, dyspepsia, diarrhea, vomiting, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH.
Dermatologic:	Pruritus, petechiae, urticaria, photosensitivity.
Other:	Polyuria, nocturia.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: erythema multiforme; leukopenia; and extreme elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been limited. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral/LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. Although individual patients may respond to any dosage level, the average optimum dosage range appears to be 180 to 240 mg/day. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

Cardizem 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1771-49). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1772-49). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

Issued 4/1/84

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NEW YORK STATE
JOURNAL OF MEDICINE

August 1984 • Volume 84, Number 8

COMMENTARIES

Treatment of severe nephrotic syndrome

Nephrotic syndrome is a pathophysiologic complex that results from increased glomerular permeability to serum proteins. Primary nephrotic syndrome of childhood, defined as minimal histologic change on renal biopsy, is uncommon. The estimated prevalence rate for this type of nephrotic syndrome is 2.3 to 2.8 per 100,000 children under 16 years of age.[1,2] Thus, the primary care physician is not likely to encounter more than two or three such children over the course of his or her practice. Considerably more prevalent, however, is secondary nephrotic syndrome associated with various types of glomerulopathy such as chronic proliferative glomerulonephritis, focal glomerulosclerosis and membranoproliferative glomerular disease.

Regardless of the overall prevalence of nephrotic syndrome, the recent trend in pediatric renal medicine is to transfer to the primary care physician increased responsibility for evaluation and management of patients with this disease. Current practice is that for children with onset of nephrotic syndrome between one and eight years of age, initial management can be provided by the primary physician. Nephrology consultation is reserved, in general, for younger children with steroid-dependent or steroid-sensitive but frequently relapsing courses, or those whose nephrotic syndrome is resistant to steroid therapy.

Thus, clinical problems associated with nephrotic syndrome such as treatment of severe (nephrotic) edema, once the domain of pediatric nephrologists in large medical centers, are managed by the primary care physician in the local hospital. However, if the primary care physician is to accept increased responsibility for direct management of children with nephrotic syndrome, unambiguous criteria must be developed to establish standards of care. In this regard, the article in this issue of the *Journal* by Weiss et al[3] on treatment of severe nephrotic edema is one of the first to establish guidelines for management of this serious complication of the nephrotic syndrome. In this report, Dr Weiss and colleagues describe their experience with treatment of severe nephrotic edema in a large number of children over a 10-year period.

Edema is the sine qua non clinical manifestation of the nephrotic syndrome; however, the use of combined intravenous salt-poor albumin and furosemide should be restricted to those children in whom edema is severe enough to threaten their overall health. An important aspect of the report is that the authors have developed clear-cut criteria for selecting which children with extensive nephrotic edema should receive this highly aggressive as well as expensive treatment regimen. Their data showed that the specific etiology of the nephrotic syndrome is not a factor in management of severe edema and, therefore, their results are applicable to all patients with severe nephrotic edema. In the experience of Weiss et al, the combination of intravenous salt-poor albumin and furosemide was shown to be more successful in producing diuresis than either modality alone or than other treatment regimens.

The treatment protocol, however, is associated with side effects that demand strict selection of patients in whom the risk/benefit ratio is understood. Nephrotic proteinuria leads to decreased intravascular volume which may vary from minimal to severe and, in markedly hypoproteinemic children, there is associated decreased renal perfusion, hyperreninemia, and hyperaldosteronemia.[4] If renal failure is not present, these children are usually not hypertensive because of the protective effect of the decreased intravascular volume. However, infusion of salt-poor albumin with resultant shift in edema fluid to the intravascular space may lead to hypertension, as was seen in the studies reported. Theoretically, infusion of a potent loop diuretic such as furosemide should counter increased vascular volume and lower the elevated blood pressure. However, factors such as edema of the kidney and the reduced renal perfusion rate may preclude or, at a minimum, significantly delay the onset of action of even the more potent diuretics. Unfortunately, the combined use of salt-poor albumin and furosemide is not easily titrated and, in my experience, hypertension occurs regularly with this type of therapy.

An additional and potentially more serious complication of this therapy was the elevation of serum creatinine in some patients. The reason for this increase was not explained but a possible cause is acute, albeit transient, tubular necrosis. The hemodynamics that precede intravascular volume depletion, characterized by hyperreninemia with possible secondary vasoconstriction and altered renal perfusion secondary to decreased intravascular volume, could result in renal tubular insult with tubular membrane damage. It is well known that the period of tubular ischemia or hypoxia is not a major factor in the production of tubular necrosis.[5] The possibility that elevated serum creatinine reflects renal damage is unambiguous, and it is incorrect to relate this elevation to "pre-renal" volume depletion which may indeed be a major consideration in the differential course of elevated serum urea nitrogen.

In view of the potentially serious sequelae of severe nephrotic edema, the demonstration by Weiss and colleagues of the effectivenes of combined intravenous salt-poor albumin and furosemide in relieving this condition is extremely important and will be a significant and useful clinical tool to the practicing physician. The authors appropriately counsel great caution in the use of this treatment regimen and offer guidelines for selecting patients whose conditions are serious enough to require this type of therapy. As emphasized above, the therapy is not without significant risks, and the selection criteria and treatment protocol should be adhered to rigorously. In my view, albumin infusion should be extended to 120–180 minutes rather than the 60 minutes suggested, and furosemide should be given at intervals during the albumin infusion as well as after the infusion, in an attempt to further decrease the possibility of serious side effects. The above comments not withstanding, I am highly enthusiastic about this important contribution to clinical pediatrics.

EDDIE S. MOORE, MD
Associate Professor of Pediatrics
University of Chicago
Pritzker School of Medicine
Chicago, IL 60616

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Diuretics in the management of nephrotic edema

The treatment of edema and ascites associated with the nephrotic syndrome has been a subject of discussion for many years. Relatively crude maneuvers such as drainage of the peritoneal cavity through a trocar were common practice only 30 years ago. This approach was necessary even though concentrated human serum albumin was already available.[1] The limiting factor may have been the type of diuretics available which, at the time, consisted of mercurials. Since their apparent mode of action resulted in some degree of tubular damage, they were not indicated in patients with renal disease. With the breakthrough of diuretics such as the chlorothiazides, followed by that of the "loop diuretics" ethacrynic acid and furosemide, the effectiveness of conservative therapy was increased and drainage of ascitic fluid became obsolete.

Physicians who were exposed to both approaches can appreciate the tremendous advantages of being conservative. Still there are potential or actual complications stemming from the use of very desirable drugs or treatment protocols. It is important that the risk/benefit ratio be established, decisions made based on complete information, and precautions taken to prevent, modify or document most aspects of a patient's response.

Various complications have been ascribed to the use of diuretics in patients with nephrotic syndrome. Excessive loss of fluids leading to dehydration, thrombosis of vessels and shock have been described.[2,3] Some physicians have used large doses without complications,[4] while others have warned against their use except in extreme and specific conditions.[5] This has led to a state of concern and confusion as to the best approach in the use of diuretics for the prophylaxis or treatment of nephrotic syndrome edema.

Most authors seem to agree that chronic oral administration of diuretics is not warranted, even in patients with frequent relapses or unresponsiveness to corticosteroids. Diuretics like furosemide, with the potential of increasing the glomerular filtration rate[6] or blood volume,[7] may have modified the general guidelines in this regard. The concurrent use of oral furosemide and metolazone offers exciting new possibilities; since they seem to have additive effects, smaller doses than usually recommended for each one may be used with greater safety and positive results. Thus, oral administration of diuretics may become more frequent. Will there also be more complications? Ideally, assessments of the use of oral diuretics should be prospective in order to acquire all the necessary data and to avoid the incompleteness of retrospective studies.

The status of the intravascular fluid compartment (IVC) deserves attention in evaluating the advantages and disadvantages of various methods of treatment of nephrotic syndrome edema. The condition of the IVC should be determined before making a decision on the most suitable method of treatment. It has been shown that patients with nephrotic syndrome may have either a normal, expanded,[8,9] or contracted[10] blood volume. Response to various treatments depends on numerous factors including the status of the IVC and various hormonal responses.[11] It has been assumed that a patient with nephrotic syndrome who has a decreased IVC will tend to have more problems with diuretic therapy (if it is effective) than a patient who has an increased IVC. If it is substantiated that furosemide does increase blood volume,[7] problems such as renal vein thrombosis[12] may be related to other effects of this drug (for example, coagulation), to complications of other drugs used concurrently, or to the natural course of the syndrome.[3,11]

In addition to the acute complications assessed in the paper by Weiss et al[13] which appears in this issue of the *Journal*, the potential danger of persistent changes induced by albumin or diuretics needs careful attention. It has been suggested that focal and segmental glomerular sclerosis may signal a persistent decline in renal function, which appears at a faster rate in patients receiving albumin and furosemide than in those receiving other forms of diuretic treatment.[14] It is also possible that the rate at which diuretics like ethacrynic acid or furosemide are administered will determine the presence or degree of renal or otological damage. The rate used by Weiss and associates to administer furosemide (1 to 2 mg/kg/20 min),[13] if effective, should be used instead of the "push" approach more commonly prescribed; an alternative of 0.2 mg/kg/min has been proposed and used effectively.[15]

The limited number and mild nature of complications described by Weiss et al correctly led them to conclude that their "therapeutic regimen was highly successful" but that this "therapy should be reserved for those patients in whom no other measures are effective in controlling nephrotic edema." Among the latter, moderate salt and fluid restriction associated with bed rest are potentially helpful recommendations.

Ideally, treatment of nephrotic syndrome edema should consist of the treatment of the underlying cause, such as elimination of allergenic or chemical agents, drugs, or infections that may contribute to or produce the condition. In addition, nonspecific treatment of the syndrome such as corticosteroid or immunosuppressor therapy should not be overlooked.[3,11] Finally, experimental approaches such as water immersion,[16] continuous hemofiltration,[17] and fasting-elemental diets[18] may point the way to new methods of treatment that would be both safe and effective.

JOSE STRAUSS, MD
CAROLYN ABITBOL, MD
GASTON ZILLERUELO, MD
MICHAEL FREUNDLICH, MD
Division of Pediatric Nephrology
Department of Pediatrics
University of Miami
School of Medicine
PO Box 016960
Miami, FL 33101

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Unanswered questions about mitral valve prolapse

The report in this issue of the *Journal* on mitral valve prolapse by Pader[1] underscores the familial nature of this entity. Mitral valve prolapse has been found to be a frequent disorder in the general population (4% to 10%).[2–4] It has been associated with symptoms of chest pain, dyspnea, palpitation and fatigue. Supraventricular and ventricular rhythm disturbances as well as progressive mitral regurgitation have been documented.[5] Yet with all of the information available about this disease, many basic questions concerning its natural course remain unanswered. Accordingly, it is often difficult to assess the significance of this abnormality in individual patients.

Given the high incidence of mitral valve prolapse in the general population, the vast majority of patients remain asymptomatic. There is no clinical marker with which to predict who will develop symptoms and who will not. It appears that the patients who have the auscultatory findings of mid-systolic murmur and click along with electrocardiographic changes are most likely to develop symptoms. The electrocardiographic abnormalities most often seen are non-specific ST-T wave abnormalities in the inferior and lateral leads. Occasionally there is prolongation of the QT interval as well. Patients who present with this "auscultatory and electrocardiographic syndrome" are in need of closer observation than those who have an isolated systolic click without electrocardiographic abnormalities.

Most population studies have been performed on young patients. Where are all the patients with a murmur and click in the elderly population? Does the incidence of mitral valve prolapse change with age? The auscultatory features probably do. The young girl with a murmur and click could be the septuagenarian with a pansystolic musical murmur of mitral regurgitation 50 years hence. In elderly patients with heart failure and murmurs of mitral regurgitation considered to be papillary muscle dysfunction, mitral valve prolapse should be ruled out as the cause of their mitral regurgitation. A population study of elderly patients would give valuable insight into the course of this abnormality.

The true incidence of complications remains a clouded issue. Are these complications specific for mitral valve prolapse, or are they chance happenings within a large population of otherwise healthy individuals? The incidence of sudden death seems to be exceedingly low, and is apparently limited to those individuals with the long Q-T syndrome (an independent risk factor for sudden death). The risk of endocarditis is elevated in some studies. Although many dental procedures may have been performed on patients with mitral valve prolapse without complications before the diagnosis was made, endocarditis prophylaxis is recommended in these individuals. The association of mitral valve prolapse with a peripheral embolus has been reported, but needs further validation.[6] Progressive mitral regurgitation occurs in up to 10% of subjects with this diagnosis. On close inspection of the valve tissue after mitral valve replacement, it is apparent that mitral valve prolapse is one of the most common causes of severe isolated mitral regurgitation.

It is clear that mitral valve prolapse is not an auscultatory or echocardiographic curiosity. It is an abnormality from which certain well-defined syndromes can be recognized, diagnosed, and treated. However, the vast majority of patients will remain asymptomatic and have a benign course. While definitive guidelines regarding the management of these asymptomatic patients do not exist, reassurance should be the cornerstone of our approach.

P. M. PROCACCI, MD
Assistant Professor
William Likoff Cardiovascular Institute
Hahnemann University Hospital
Philadelphia, PA 19148

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Strongyloidiasis: a dangerous opportunistic infection

Strongyloides stercoralis is an intestinal nematode found throughout the world in both warm and temperate climate zones. However, the infection it causes is relatively uncommon in the United States.[1] Many intestinal infections with this parasite are asymptomatic; heavier infections produce a variety of non-specific complaints including abdominal pain, weight loss and diarrhea. The definitive diagnosis of the infection can be made only through the demonstration of one of the stages of the parasite in either the stool or duodenal aspirate and less frequently in sputum. Often, repeated stool examinations are negative. Thus many stool samples may be required to make the diagnosis of intestinal strongyloidiasis.

Unlike most other intestinal helminths, *S stercoralis* has the unique ability to re-infect its host without passing through an external environmental cycle. Rhabditiform (non-infective) larvae can metamorphose in the intestinal tract of the host into filariform (infective) larvae and thus keep the infection patent for several decades.[2] This autoinfection, which is characteristic of the parasite, poses special risks for patients with either impaired cellular or humoral immunity.

Hyperinfection of the intestinal tract and systemic strongyloidiasis have been documented in patients with conditions such as protein-calorie malnutrition, lepromatous leprosy, cancer, severe burns, radiation illness, and cirrhosis. Impairment of humoral immunity, as found in those with hypogammaglobulinemia, has also been documented as a major risk for hyperinfection and systemic disease.[3–6] Patients in whom hyperinfection or systemic disease or both occur often do not respond favorably to therapy with thiabendazole, the drug of choice, which is effective in routine infections.[5]

The use of adrenocorticosteroids and other immunosuppressive drugs such as azathioprine and cyclophosphamide can cause either hyperinfection or systemic disease in patients with intestinal strongyloidiasis.[3,4] The report by Kimmelstiel and Lange[7] in this issue of the *Journal* clearly demonstrates that even a short course of treatment with an adrenocorticosteroid in a patient with unsuspected intestinal strongyloidiasis can result in systemic disease, which in this instance was fatal. Although many such cases of strongyloidiasis have been documented following several months of adrenocorticoid therapy, it should be noted that even short courses of these drugs as well as topical application in the eyes can produce either hyperinfection or systemic disease.[8,9]

The report by Dellacona et al[10] in this issue of the *Journal* illustrates hyperinfection of the organ system usually parasitized by *S stercoralis*. Because of the patient's return to an endemic area, it is impossible to interpret the 20-year long history of strongyloidiasis as being the result of either autoinfection, re-infection or both. The reasons for the patient's hyperinfection remain obscure, and it is difficult to characterize definitively the five previous episodes of rectal bleeding as being due to hyperinfection.

Although the patient's cellular immune profile is not available, it may ultimately reveal the presence of a disease associated with cellular immune deficiency.

It has been known for some time that parasitic diseases in and of themselves can cause immunosuppression. Williamson and Greenwood[11] demonstrated that the immune responses to typhoid, and meningococcal vaccines and tetanus toxoid were depressed in children suffering from acute malaria. The mechanism of this immunosuppression and that observed with other parasitic infections is not fully understood.[12] Malaria appears to induce suppression of the immune response to parasite unrelated antigens, whereas diffuse cutaneous leishmaniasis seems to suppress parasitic-specific antigens.[13]

These recent findings have been augumented by the observation on Okinawa (Japan) that a high percentage of people with intestinal strongyloidiasis are carriers of human T-cell leukemia virus (HTLV).[14] Because cellular immunity is impaired in patients with adult T-cell leukemia (ATL), and cell-mediated immunity is suppressed in HTLV carriers, hyperinfection and systemic strongyloidiasis are constant threats.[14] Nakada et al[14] suggest two possible explanations for the association between HTLV carriage and strongyloidiasis. The impairment of immunity associated with HTLV may allow the parasite to proliferate and thus facilitate its detection. Alternatively *S stercoralis* may promote HTLV infection over time, resulting in HTLV antibodies.[14]

Gill and Bell[15] interpret the high prevalence of HTLV antibody on Okinawa as the result of immunosuppression due to *S stercoralis*. They convincingly sustain this hypothesis with data gathered from observations of British ex-Far East prisoners of war who had been infected with *S stercoralis*. These findings may have relevance to the case reported by Dellacona et al.

Recent research on disseminated strongyloidiasis in patas monkeys has demonstrated no correlation between the degree of immune response and the course of infection. Animals die of disseminated disease despite the presence of humoral and cellular antibodies to parasite-specific antigens. These findings suggest that other factors such as local intestinal immune and nonimmune mechanisms may protect against disseminated strongyloidiasis.[16] Clearly host response to *Strongyloides stercoralis* is a complex matter that is only partially understood at present.

Both reports in this issue illustrate the need for a high index of suspicion about strongyloidiasis in individuals who once spent time in endemic areas of the world. This holds true even for those patients who left an endemic area decades ago. Diagnostic efforts must be especially diligent in immunocompromised patients and in those about to undergo immunosuppressive therapy of any kind, even if it is to be for only a short period of time. Despite such efforts, it is sometimes not possible to establish the existence of the infection. Prior to the institution of immunosuppressive therapy in proven cases, appropriate treatment with thiabendazole should be given and eradication of the infection definitively confirmed. Failure to carry out these simple, but meticulous steps may result in serious and even fatal consequences in patients who harbor even low-grade strongyloides infections.

PASCAL JAMES IMPERATO, MD
Deputy Editor
Professor and Chairman
Department of Preventive Medicine
and Community Health
State University of New York
Downstate Medical Center
New York City, 11203

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MSSNY APPLAUDS PASSAGE OF NEW LAW

The following statement was issued in June by the Medical Society of the State of New York following the Senate's passage of a bill requiring automobile drivers and front-seat passengers to use seat belts:

> The Medical Society of the State of New York has long urged such legislation as a public health measure, and in 1982 joined with the American Association for Automotive Medicine to create the New York Coalition for Safety Belt Use to work actively towards that end.
>
> Physicians more than most people know the terrible toll paid by unbelted occupants in motor vehicle crashes. In hospital emergency rooms throughout the state, they see victims with crippling and disfiguring injuries that could have been minimized or avoided entirely if the motorist had used safety belts.
>
> The facts are indisputable. Widespread belt use could cut deaths and injuries in half, according to the experience in countries where seat belt laws are in effect.
>
> Moreover, we believe that the public is ready and willing to support such a law. MSSNY conducted a survey on the subject at its exhibit during last year's New York State Fair in Syracuse. More than 67% of 13,492 persons who filled out a questionnaire indicated they favored a mandatory safety belt law.
>
> To those who argue that such a law is an infringement on civil rights, there are two answers: The first is that society bears much of the financial burden of auto injuries through higher automobile and life insurance premiums, welfare bills, Social Security payments, and high health care costs.
>
> The second answer is that the unbelted driver risks not only his life, but the lives of others around him. He can be thrown away from the wheel of his vehicle, causing it to go out of control. No one has a right to endanger other people.
>
> Senator Norman J. Levy and Assemblyman Vincent J. Graber, co-sponsors of the legislation, and their colleagues who are supporting the measures deserve high credit. They have the wholehearted support of the 27,000 physician members of the Medical Society of the State of New York.

Governor Cuomo signed the bill on July 12, 1984, and it becomes effective on January 1, 1985. The bill carries a $50.00 fine for individuals caught without seat belts.

LETTERS TO THE EDITOR

Address correspondence to Editor, New York State Journal of Medicine, *420 Lakeville Road, Lake Success, NY 11042. Letters should be typed double-spaced and include the signature, academic degree, professional affiliation, and address of each author. Preference is given to letters not exceeding 450 words, and every effort will be made to assure prompt publication. All letters are personally acknowledged by the Editor.*

Pets as carriers of streptococci

TO THE EDITOR: In reply to the article, "Cherchez le chien" by Stuart M. Copperman, MD (*NY State J Med* 1982; 82: 1685–1687), I would like to make the following comments. According to the author's own sources, in 1980 Biberstein et al[1] complained that existing information on the laboratory aspects of beta-hemolytic streptococci from dogs is fragmentary and contradictory. Crowder et al[2] concluded that it was unlikely that the household pet would play a major role in the maintenance of streptococcal disease in the family group.

Group G beta-hemolytic streptococcus is a normal organism in the throat of the dog. Group G and A beta-hemolytic streptococci have antigenic similarities that can be extremely difficult to distinguish. To be definitive, one would also have to know the media the organism was grown on. For example, on phadelac assay they may react similarly, and trying to extrapolate from one species to another is impossible. One also has to consider that a reference to group A beta-hemolytic streptococci only identifies the carbohydrate antigen. In order to define the type of streptococcus more thoroughly, the "M" or protein antigen would have to be known. The obvious implication is that routine cultures done in physicians' or veterinarians' offices are not the definitive answer to implicating the family pet as the source of streptococcal infection in humans.

The last sentence in the article says it all. The author quotes Schauffler[3] as stressing the importance of pets in maintaining human health and advising physicians to "think twice before using them unfairly as sacrificial goats or vehicles of their own prejudices."

WILLIAM F. STACK, DVM
Limestone Plaza
Fayetteville, NY 13066

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In reply: Dr Stack's comments are well taken. However, many cultures taken early in the course of the study were done by certified clinical laboratories; later ones were done in the office using the methods described in my original article. Cultures from control studies by two veterinarians were tested only by certified laboratories. To the best of our knowledge, they were accurate within the limits Dr Stack describes.

Feedback from throughout the country has been incredible. When cultures were done on pets of families with *recurrent* Group A streptococcal sore throats, physicians and veterinarians have reported, by phone and mail, similar results.

Certainly, culturing a pet in such an instance can do no harm. I have been a pet-owner (and pet-lover) all my adult life, and am fully aware of the value of pets in a home. In no way am I denigrating any of "Man's best friends," nor am I advocating their removal from the home. On the contrary, I very often recommend pet ownership to my patients.

Finally, Dr Stack quotes the literature accurately. However, that which is written is not necessarily so. An open-minded approach by pediatricians, family practitioners *and* veterinarians, and a willingness to culture pets (and treat positives) in homes with otherwise unexplained recurrent strep throats, will provide answers. I eagerly await communications from physicians who have applied my report to their practices, as well as future controlled studies to confirm these observations.

STUART M. COPPERMAN, MD
3137 Hewlett Ave
Merrick, NY 11566

Adnexa, not adnexae

TO THE EDITOR: The purpose of language to convey meaning and thought may be hampered by errors in spelling and usage. Due to misunderstanding and mistaken derivatives, the word "adnexa" is frequently a victim of inappropriate use. A recent article in the *Journal*[1] highlights the problems associated with this word and contains an incorrect form, adnexae.

Adnexa is a word used only in the plural to mean conjoined, subordinate or associated parts. When its use refers to appendages of the uterus, adnexa means fallopian tubes and ovaries and, possibly, other adjacent structures.[2–4] The origin of this word is in the Latin roots meaning joined and to. The terminal "-a" in a word derived from Latin is not rare and reflects a second declension neuter noun whose singular nominative form, if it existed, would end in "-um." Thus, the singular form of the word in question would be adnexum, but recent written reference with this usage of the singular has not been found, although it does appear in dictionaries[5,6] and in a classic reference[7] where it is not used for structures adjacent to the uterus. Clear application of the term adnexum requires an unusual situation, and this word should rarely, if ever, be used.

The use of the word adnexa to connote a single structure is awkward at best, especially in reference to any one of those structures contiguous or attached to the uterus. Since there are numerous named structures which are appendages to the uterus, it would be most infrequent to find the need to have a neutral, nonspecific, singular term of reference when more specific words abound, such as fallopian tube, ovary and peritoneum. The requirement, however, for an encompassing word to name the varied but geographically related structures is frequent—neoplasms of the adnexa, inflammation of the adnexa, palpation of the adnexa.

The error in assuming that adnexa is

a singular word arises from the lack of a terminal "-s" which, of course, marks the plural for most words in English, or, to mistaken attribution of the word's origin to a first declension feminine singular noun. The author or speaker who uses adnexae implies that this is a word of Latin derivation, mistakes adnexa for the singular and compounds the error by creating an inappropriate form representing a first declension feminine plural. In the article cited,[1] further ambiguity is engendered since a unilateral group of structures is described and the incorrect use of adnexae may suggest that the authors are referring to bilateral structures. Most impressive is the consistency of the authors in trying to justify their inappropriate use of language: their references include a report[8] in which the word adnexa appears in the title, referring to those structures unilateral to the uterus (tube and ovary); in their bibliographic reference to the earlier article, the word adnexa, as correctly used by the prior author, is changed and rewritten adnexae, an error in both bibliographic accuracy and English usage.

Appropriate use of the word adnexa is easily found,[9] but, curiously, several definitive works omit the use of the word entirely.[10-12] The error discussed here has attracted attention before,[13] and its correction may still need reiteration for both authors and editors.

In general, usage determines meaning, and the evolution of language reflects the impact of common use. But the importance of clarity and accuracy in medical terminology demands a most conservative approach to the use of language, lest meaning be lost.

The correct and appropriate use of the word adnexa should be commended to students, physicians and editors.

ROBERT C. WALLACH, MD
Department of Obstetrics & Gynecology
Beth Israel Medical Center
10 Nathan D. Perlman Place
New York, NY 10003

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In reply: Mea culpa, mea culpa, mea maxima culpa.

WILLIAM J. MANN, MD
Department of Obstetrics and Gynecology
School of Medicine
Health Sciences Center
SUNY at Stony Brook
Stony Brook, NY 11794

Fluoridation controversy

TO THE EDITOR: I have several reactions to the article "After 40 years, no signs of decay in fluoride controversy" (*NY State J Med* 1984; 84:203-205).

Chemical hypersensitivity *does* exist and does, by definition, involve about 1% of exposed individuals. It is to be distinguished from toxicity when a large percentage of the individuals exposed exhibit adverse reactions.

In 1983, at a conference on nutrition in Boston, MA, I attended a workshop at which fluoridation was being championed. I asked a question of the two speakers: "How many glasses of water must the average youngster drink day after day to obtain the proper amount of fluoride?" The answer, "six to eight," upset quite a few in the audience. We later agreed that none of us knew of any child who drank that much water a day.

Why does water fluoridation continue to be an emotional, socio-political issue? There are several alternatives that are more effective than bathing or showering in fluoridated water: (1) a direct application by one's dentist; (2) the use of fluoridated toothpaste; (3) the use of children's multivitamin tablets. In fact, as an ecologist, I am concerned about the concomitant use of the multiple sources of "optimal" dosification available.

To paraphrase the humorist James Thurber, who stated, upon learning that his water was being fluoridated, "Just because there are tens of millions of constipated Americans is no reason for any governmental authority to put Milk of Magnesia in my drinking water!"

JUAN WILSON, MD
1900 Hempstead Turnpike
East Meadow, NY 11554

TO THE EDITOR: I read with interest the article, "After 40 years, no signs of decay in the fluoride controversy."

John Small, fluoridation information specialist for the National Institute of Dental Research, attempted to refute my statement that the majority of scientific opinion is against fluoridation, claiming that "every developed country supports fluoridation." In fact, fluoridation has been discontinued, rejected or banned in most of Europe. Less than 2% of the water supply of Western Europe is fluoridated. I would like to see citizens in this country receive the same protection.

Although the article did not cover it, I had emphasized to the author that total fluoride intake has increased to such high levels that even proponents of fluoridation have expressed concern. Fluoride is reaching us through foods and beverages manufactured or processed in fluoridated areas, as well as through toothpastes, pharmaceutical products, factory emissions, automobile exhaust, insecticides, fertilizers, and many other sources. My primary concern is chronic fluoride toxicity from day to day ingestion over a long period of time.

I do appreciate the *Journal*'s attempt to present both sides of the issue. I now ask that it recognize the legitimacy of this controversy and reexamine the issue of fluoridation and fluoride's effects on the body, just as the New York City Council Health Committee has done.

In my opinion, the appropriate solution is for fluoride to be administered and obtained on a one to one level between doctor and patient, as with all other drugs, and not added to public water supplies. Fluoridation is a practice which does not allow for biological individuality among people, or differences in age, weight, sex, intolerances, or state of health.

PAUL STEPHEN BEEBER, JD
New York State Coalition
Opposed to Fluoridation
101 Bay Ave
Hicksville, NY 11801

Chemical disclosure laws

TO THE EDITOR: Chemical hazards emanating from the workplace present a major, growing public health menace in the United States. The National Institute of Occupational Safety and Health Registry of Toxic Effects of Chemical Substances lists over 39,000 chemicals. Each year, about 1,000 new chemicals are marketed.[1] An estimated 150 to 275 million metric tons of hazardous wastes are produced annually.[2] Many people are exposed to these toxins. Approximately 40 to 50 million people are exposed to hazardous chemicals that are regulated by the Department of Labor.[3] Chemical exposure may be associated with significant health harms: about 162,000 new cases of occupational illness were reported by the Bureau of Labor Statistics in 1977, and 143,500 more were reported in 1978.[4] An unknown number of neighboring residents may have been harmed because of exposure to chemicals emitted from the workplace.

New York State has responded to the public health danger presented by occupational chemical toxins. In June 1980, a state chemical disclosure ("right to know") law was enacted.[5-6] The law provides for the establishment of an outreach and informational program for workers, and for investigations to study toxic substances in the workplace. Employers, upon employee request, must provide information about specific chemical identification, acute and chronic effects of exposure, the symptoms of such effects, and appropriate emergency treatment. Unfortunately, the state's "right to know" law, is limited in scope, protecting workers rather than the general public. However, an Executive Order issued by Governor Cuomo in December 1983 extends protection against chemical hazards to community residents.[7] The order provides for industrial surveys of chemicals, intended in part to inform the public of dangers posed by chemical dumps in their communities.

A federal "right to know" standard was issued in November 1983.[3] The federal standard is less protective of the public health than existing state measures. It applies only to workers in the manufacturing sector, which in 1978 represented less than 30% of total employment.[4] The federal standard also does not require that information about chemical hazards be disclosed to the general public. The effects the federal standard will have on New York State law is unclear. Since the federal standard is limited to protecting workers in manufacturing, state workers outside of manufacturing will probably remain under the protection of the state law. The federal standard should not affect the Governor's Executive Order.

Chemical disclosure laws raise major public health policy issues. The active participation of the medical community is vitally important to the humane, informed resolution of these issues.

LEO UZYCH, JD, MPH
103 Canterbury Drive
Wallingford, PA 19086

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4. US, Federal Register 47, 12092 (March 19, 1982).
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6. US, Labor Law, Article 28, §875 et seq (McKinney's 1980).
7. New York, State of New York Executive Order, no. 33 (December 29, 1983).

CORRECTION

In the article by Fleisher et al entitled "Acute appendicitis in a patient with concurrent adenocarcinoma and carcinoid tumor of the appendix" (NY State J Med 1984; 84:321-322), Figures 1 and 2 were reversed.

The New York Medical Political Action Committee and the American Medical Political Action Committee will co-sponsor a one-day symposium, "Physicians and Political Action," that will focus on ways that physicians can become more active in the political process. The symposium, to be held on Thursday, September 20, 1984 from 8:30 am to 4:00 pm at The Executive Inn, Buffalo, will feature representatives from the New York State Assembly and Senate, as well as members of Congress and congressional candidates.

Treatment of severe nephrotic edema with albumin and furosemide

ROBERT A. WEISS, MD, MORRIS SCHOENEMAN, MD, IRA GREIFER, MD

ABSTRACT **Treatment of severe nephrotic edema with intravenous administration of salt-poor albumin and furosemide has gained acceptance without proper investigation of its effectiveness and complications. To evaluate these aspects, we examined the results of 404 courses of therapy administered to 24 children with nephrotic syndrome: 10 with minimal change, 11 with focal segmental glomerulosclerosis and three with other histopathology. Each course of therapy consisted of 25% albumin solution, approximately 1 g/kg, followed by furosemide, 1 to 2 mg/kg, intravenously. The mean number of courses per patient was 17.7 ± 20 and the mean duration of therapy was 11.25 ± 7.1 days. Diuretic response was not correlated with serum albumin or creatinine concentrations or with histologic diagnosis. Complications of therapy included acute hypertension in 10 patients and a significant rise in serum creatinine in four patients.**

(NY State J Med 1984; 84:384–386)

INTRODUCTION

The morbidity and mortality due to the nephrotic syndrome have decreased with the use of adrenocorticosteroids and antibiotics. However, massive edema remains a major problem. Nephrotic syndrome has been associated with peripheral[1] and renal venous thrombosis,[2] respiratory distress due to mechanical compression from ascites or pleural effusion, and cardiovascular collapse secondary to intravascular volume depletion.[3] Other complications encountered in the edematous nephrotic patient include abdominal pain with and without peritonitis, skin breakdown, and increased susceptibility to infections.

Therapy for nephrotic edema has been directed at the two major pathophysiologic disturbances, hypoalbuminemia and renal sodium retention. Administration of albumin alone produced a variable and transitory diuretic response, probably because the decrease in fractional reabsorption of filtered sodium at the level of the proximal tubule induced by volume expansion was counteracted by increased reabsorption at more distal sites.[4] Diuretic drugs such as chlorothiazide and furosemide, when used alone, may not be successful, perhaps because enhanced proximal reabsorption under the stimulus of reduced effective arterial volume allows little sodium to be delivered to the distal nephron, where these agents are active. Combining the infusion of salt-poor albumin with furosemide should restore, at least in part, the intravascular volume, increase distal delivery of salt, and thus create the conditions required for loop diuretics to exert their effect.

PATIENTS AND METHODS

Of 202 patients with nephrotic syndrome seen at the Hospital of the Albert Einstein College of Medicine during a 10-year interval, 41 were admitted to the hospital solely for the management of edema with intravenous albumin (A) and furosemide (F) therapy. Of the 41 patients who received A-F therapy, we excluded 15 because of insufficient data concerning the degree of diuretic response. We also excluded two patients who responded to adrenocortical steroids within one week after the initiation of A-F therapy, because diuresis may have been due to the former.

The 24 patients who met our criteria ranged in age from 2.3 to 22.5 years at the time they received A-F therapy. There were 15 boys and nine girls. Diagnoses of the primary glomerular disease were distributed as follows: 10 children had minimal change nephrotic syndrome (MCNS), 11 had focal segmental glomerulosclerosis (FSGS), and three had other histopathologic conditions (focal, global sclerosis; proliferative glomerulonephritis with mesangial sclerosis; and focal tubular necrosis). All patients had received prednisone initially, and 16 of the 24 had received cytotoxic therapy (cyclophosphamide, nitrogen mustard, or azathioprine) at one or more times during the course of their disease. No patients were receiving such therapy at the time of hospitalization for A-F treatment.

There were a total of 51 admissions, during which these patients received A-F therapy 404 times. Eleven patients were admitted to the hospital for this therapy on multiple occasions; 13 patients had one admission each. Indications for A-F therapy included anasarca, massive ascites, respiratory distress due to ascites or pleural effusions, massive scrotal edema, skin breakdown related to edema, and peritonitis with ascites.

On admission to the hospital, the patients were given a diet restricted in sodium (0.5 g for prepubertal children and 1 g for adolescents) but allowed fluids ad libitum. Oral diuretic agents were discontinued. Blood urea nitrogen (BUN), creatinine, and serum albumin were measured. Therapy consisted of intravenous infusion of 25% salt-poor albumin, 1 g/kg body weight per dose given over a period of 30 to 60 minutes. Furosemide (1 to 2 mg/kg body weight per dose) was usually administered 30 minutes after the albumin infusion was completed (range 15 to 60 minutes), but occasionally it was given during the albumin infusion. This regimen was used repeatedly (one to three times per

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From the Children's Kidney Center of the Hospital of the Albert Einstein College of Medicine (Drs Weiss and Greifer) and the Division of Pediatric Nephrology, Department of Pediatrics (Dr Schoeneman), Albert Einstein College of Medicine, Yeshiva University, Bronx, New York.

Address correspondence to Dr Greifer, Director of Pediatrics and the Children's Kidney Center, The Hospital of the Albert Einstein College of Medicine, 1825 Eastchester Rd, Bronx, NY 10461.

24 hours) over several days, depending on the diuretic response and clinical status of the patient.

Detailed records of fluid balance were unavailable for the majority of our patients. Rapid loss of body weight during A-F therapy was used to calculate the diuretic response. In an attempt to identify factors that might predict the outcome of treatment, we analyzed the relationships between age, hematocrit (as an index of plasma volume contraction), serum albumin, BUN, serum creatinine concentration, and histopathology with respect to weight loss during the initial 48 hours of A-F therapy as well as the entire duration of therapy. Complications concurrent with, or immediately following, therapy were recorded and their frequencies were calculated separately for each histopathologic group.

Statistical analysis of data was performed by Chi square and Student's t-tests. Results are reported as the mean plus or minus the standard deviation.

RESULTS

A-F therapy was administered for 11.25 ± 7.1 days per patient. The mean number of treatments per patient was 17.7 ± 20. The percent weight loss per patient was 13.6 ± 8.4 per hospitalization and 2.46 ± 2.22 per A-F administration. There was no significant difference between the MCNS and FSGS patients with respect to diuretic response. The 10 patients with MCNS required only 14 hospitalizations for edema management, whereas 34 hospitalizations were needed by the 11 patients with FSGS.

Among the 11 patients with multiple admissions, nine responded during the first hospitalization and during 21 of 22 subsequent admissions. The other two patients, both with MCNS, failed to respond to therapy during their first hospitalization and did not respond on their subsequent admission. Thus, response or failure of response was consistent in each patient. No correlation was found between an individual patient's response to therapy and age, renal histopathology, blood pressure, BUN, or serum creatinine on admission. Serum albumin was 1.76 ± 0.31 g/dL (range, 0.5 to 2.6 g/dL). Mean hematocrit was 34.8% ± 8.2%, (range, 20% to 55%). The ratio of hematocrit to serum albumin, used as an index of contracted plasma volume and hemoconcentration, did not correlate with the diuretic response ($r = 0.15$).

Sudden onset of hypertension and a sudden increase in serum creatinine concentration were the major complications associated with A-F therapy. On admission, hypertension (diastolic blood pressure >95th percentile for age and sex[5]) was noted in 13 patients. During albumin infusion, acute hypertension (diastolic blood pressure ≥100 mm Hg in a formerly normotensive patient) was noted at least once in 10 patients. Exacerbations of hypertension were noted in five of the 13 patients who were hypertensive on admission, although no patients became symptomatic. Parenteral treatment with hydralazine was required in two patients; in the remainder, the condition resolved spontaneously within one to four hours after the A-F infusion was terminated. The occurrence of hypertension never mandated discontinuation of therapy.

The serum creatinine concentration on admission was elevated (>95th percentile for age and sex[6]) in 13 patients, nine of whom had the diagnosis of FSGS. A sharp increase in serum creatinine concentration coincident with A-F therapy was noted in four patients (Fig 1). We were unable to correlate diuretic response with changes in serum creatinine. No contrast media or nephrotoxins were administered, and only one patient became oliguric. In one patient we were able to document an increase in serum creatinine concentration with A-F therapy and a partial resolution when the therapy was discontinued, followed by a second increase in serum creatinine when A-F therapy was re-instituted (Fig 1).

Other complications included first-degree heart block in one patient, moderately severe hypokalemia (2.3 mEq/L) in a second, and metabolic alkalosis (serum bicarbonate concentration >28 mEq/L) in six others. In one patient swelling and erythema of the hand developed at the site of albumin infusion together with lymphangitis and purulent exudate from nail beds of the same hand on two separate occasions. Cultures were negative, and the lesions resolved spontaneously.

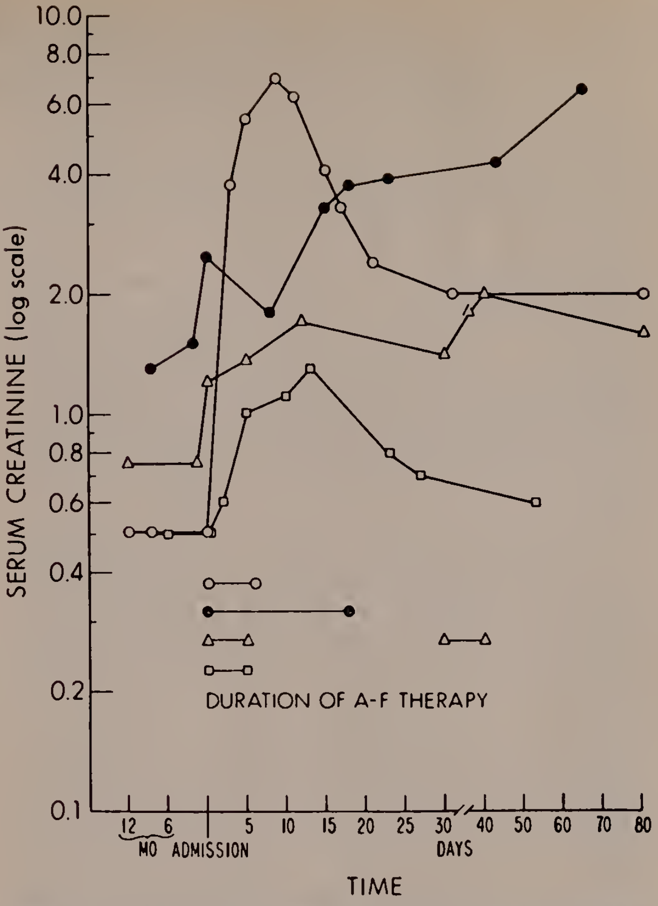

FIGURE 1. Four patients in whom serum creatinine increased coincident with A-F therapy. In two patients, serum creatinine decreased several days after therapy was discontinued, but not to pre-therapy values. One patient (△) underwent a second course of A-F therapy, with a second increase in serum creatinine concentration.

DISCUSSION

This therapeutic regimen resulted in rapid reduction of the edema in most, but not all, of the patients. We were unable to predict treatment success or failure based on clinical and laboratory data obtained at admission. Accurate estimation of extracellular fluid expansion could not be derived from our data. Prednisone therapy results in an increased body weight to height ratio. This invalidates the concept of an "ideal" weight (50th percentile) for height as a measure of the non-extracellular fluid expanded state.

A multitude of factors is involved in the distribution of infused albumin and its role in increasing delivery of sodium chloride to the distal nephron which, in turn, can effect the diuretic response of a particular patient. These include loss of administered albumin into the intracellular compartment,[7] dilution of infused albumin by extracellular fluid,[8] and transcapillary albumin leak.[9-11] In addition, poor initial response may be due to a higher concentration of, or a greater tubular sensitivity to, aldosterone in some patients than in others. The factors that affect an individual patient seem to be consistent, however, since response or nonresponse on the initial admission predicted the behavior of subsequent hospitalizations.

Severe hypertension as a complication of therapy was seen on at least one occasion in 10 patients. This finding was usually transient and often responded to a decrease in the rate of albumin infusion or to the administration of furosemide. Because of acute hypertension, parenteral administration of hydralazine was required on two occasions; more potent antihypertensive agents were never required. Hypertension was not considered severe enough to warrant discontinuation of the albumin infusion.

We observed a significant but transient increase in serum creatinine in one patient and a persistent increase in serum creatinine in three others—all with the diagnosis of FSGS. Since most of the patients were undergoing rapid changes in fluid balance, and serum creatinine is a reliable indication of the glomerular filtration rate (GFR) only in the steady state,[12] we cannot state definitively that the increase in serum creatinine concentration was consequent to a decrease in the GFR, although this explanation seems likely.

Alternatively, the increase in serum creatinine could be due to intravascular volume contraction from the marked diuresis seen in many of our patients. However, we were unable to correlate the degree of weight loss with changes in serum creatinine concentration. Moreover, in three of the four patients serum creatinine concentration remained increased even when a new steady state was reached.

Less likely explanations for the decrease in the GFR include direct nephrotoxicity of albumin or furosemide, or hypersensitivity to either of these drugs. We could find no evidence to support either of these possibilities. There are reports of reversible renal failure due to acute interstitial nephritis in association with the long-term administration of diuretics such as furosemide and thiazides. These patients had systemic signs of hypersensitivity reactions such as fever, rash and eosinophilia, and biopsy findings that were consistent with the diagnosis of acute interstitial nephritis.[13,14]

The development of a hypokalemic, hypochloremic metabolic alkalosis in several patients resulted from vigorous diuretic therapy with furosemide. This drug inhibits active chloride transport in the thick ascending limb of the loop of Henle, resulting in chloride depletion and increased reabsorption of bicarbonate by the tubule. Hypokalemia consequent to increased urinary potassium excretion is commonly seen with diuretic agents due to an increase in urine flow rate. This biochemical disturbance is corrected by administration of potassium chloride.

Patient morbidity in nephrotic syndrome is often due to complications of edema. Selection of patients for A-F therapy was based on the mechanical effects of edema (respiratory embarrassment due to ascites and pleural effusions), potential risk of severe infection and inability to manage edema on an outpatient basis with dietary sodium restriction and diuretics. Response to the A-F therapeutic regimen was usually prompt and resulted in restoration of extracellular fluid volume in most patients.

Considering the potentially devastating effects of severe edema, especially peritonitis and sepsis, we believe that the therapeutic regimen was highly successful. The vast majority of patients had partial or complete resolution of edema in several days and could return to their normal activities. Side effects such as hypertension and electrolyte disturbances are acceptable with appropriate monitoring.

TABLE I. Criteria for A-F Therapy

Respiratory compromise due to pleural effusion or massive ascites.
Massive scrotal edema that interferes with ambulation.
Peritonitis with massive ascites
Skin breakdown due to edema

TABLE II. A-F Treatment Protocol

Pre-therapy laboratory evaluation
  BUN, creatinine
  Serum albumin
  Hemoglobin/hematocrit
Administration of A-F
  Cardiac monitor
  1 g/kg salt-poor albumin over one hour; monitoring BP every 15 minutes during infusion
  1 mg/kg furosemide over 20 to 30 minutes to start at termination of albumin infusion
  Repeat no more frequently than every 8 hours
On-going monitoring
  Daily weights
  Strict records of intake and output
  Daily chemistries

The decrease in renal function seen in four patients with serious glomerulopathies remains unexplained. A-F therapy should be reserved for those patients in whom no other measures are effective in controlling nephrotic edema. Specific recommendations for the use of A-F therapy are outlined in Tables I and II.

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Correlation of serum lipid levels with cardiac and cerebrovascular disease in the aged

MANUEL RODSTEIN, MD, RICHARD R. NEUFELD, MD, JUDITH NADELMAN, M PHIL

ABSTRACT The correlations of serum lipid levels with age, cardiac status and cerebrovascular disease were studied in a group of 100 women aged 67 through 104 years. Thirty-four had no clinical evidence of any form of heart disease, 37 had clinical evidence of coronary heart disease and 29 had clinical findings of heart disease without evidence of coronary heart disease. Twenty-eight had evidence of cerebrovascular disease. Total and low-density lipoprotein (LDL) cholesterol were lower at successively advancing ages. High-density lipoprotein (HDL) cholesterol, triglycerides and the ratio of total cholesterol to HDL cholesterol showed little change. Mean lipid levels were not related to clinical evidence of coronary heart disease or cerebrovascular disease. Among those with clinical coronary heart disease and cerebrovascular disease, the mean levels of total and LDL cholesterol and log triglycerides were elevated.

(NY State J Med 1984; 84:387–389)

INTRODUCTION

Cardiovascular and cerebrovascular diseases are the greatest causes of mortality in the aged. Their correlations with serum lipid levels are of great interest, since the latter have been shown to be significant risk factors for these conditions in younger age groups.

Plasma total cholesterol and low-density lipoprotein cholesterol increase with age and peak at about age 65. High-density lipoprotein cholesterol and triglycerides also rise with advancing age.[1] Data is scanty for persons over age 65.

Since the incidence of coronary heart disease is directly related to the level of total and low-density lipoprotein (LDL) cholesterol and triglycerides and inversely related to the levels of high-density lipoprotein (HDL) cholesterol, one would expect to find high levels of the former and low levels of the latter among individuals of advanced age. Low levels of high-density lipoprotein cholesterol have been reported among persons with a history of strokes.[2,3]

This cross-sectional study of a well controlled female population in a long-term facility for the aged extends the data on serum lipid levels from the sixth into the 11th decade of life and evaluates their relationship to cardiovascular and cerebrovascular disease.

PATIENTS AND METHODS

Study population. The Central House Division of The Jewish Home and Hospital for the Aged of New York is a long-term care institution.

A comprehensive examination is performed on admission and annually thereafter. It includes a history and physical examination, electrocardiogram, chest x-ray, complete blood count and urinalysis. An automated SMA 26 blood chemistry is done on admission and again annually. Additional tests and consultations are performed on admission and at regular intervals as indicated. Reports of prior hospitalizations, private and clinic medical care, and time spent in institutions are obtained.

One hundred women aged 67 through 104 years were selected for the study. They were chosen at random so as to provide a gradually increasing age distribution in which 25 cases were between 67 and 75 years of age, 25 between 75 and 85 years of age, 25 between 85 and 95 years of age, and 25 between 95 and 105 years of age.

The majority of the residents are on a daily diet limited to 2,000 calories and 2 g sodium, with an average of 400 mg of cholesterol. When grouped by age decade, the residents' average weight is approximately 21% less than the weight of their counterparts not residing in the home.[4] Two percent of the cases drink the equivalent of 30 cc of whiskey or less a day, and 6% smoke an appreciable number of cigarettes.

Twenty-four residents were receiving treatment for congestive heart failure. Approximately 50% of the residents are on diuretic agents. Three residents had blood pressure readings of more than 160/90 mm Hg. Twenty-one had diabetes mellitus.

The patients were divided into three subgroups on the basis of cardiovascular status.

The first subgroup consisted of 37 patients with a history of clinical or laboratory evidence of coronary heart disease. This was based on a history of angina, acute myocardial infarction, diagnostic electrocardiographic changes, or a combination of these.

The second subgroup consisted of 29 patients with clinical findings of heart disease but without laboratory or clinical evidence of coronary heart disease. Included in this group were cases with congestive heart failure, systolic cardiac murmurs of grade 3/6 or greater intensity, any diastolic murmur, cardiac enlargement on chest film, atrial fibrillation or flutter, supraventricular tachycardias, intraventricular conduction disturbances, or complex ventricular extrasystoles.

The third subgroup consisted of 34 patients who had no clinical or laboratory evidence of any form of heart disease.

The patients were also divided into subgroups on the basis of cerebrovascular status. They consisted of 28 patients with a history of a prior cerebrovascular accident or transient ischemic attacks, or both and 72 cases without such findings.

Laboratory methodology. The fasting serum lipid determinations were performed in our laboratory using reagents obtained from the Dow Chemical Company, Dow Diagnostics, Indianapolis, Indiana.

The procedures followed were in accordance with the ethical standards of the committee on human experimentation of the institution in which the experiments were done.

Statistical methods. Simple correlation coefficients (Pearson's product moment) were calculated to determine the relationship between age and serum lipid levels for the group as a whole and for each of the subgroups. The relationship of serum lipid values

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From the Medical Department of The Jewish Home and Hospital for Aged, New York.

Address correspondence to Dr Rodstein, Director of Medicine and Cardiology, Kingsbridge Center of The Jewish Home and Hospital for the Aged, 2545 University Ave, Bronx, NY 10468.

TABLE I. Mean Lipid Values of Total Group (N = 100)

	Mean	Standard Deviation	Range
Age (years)	84.45	±10.65	62–104
Total cholesterol (mg/dL)	219.5	±53.80	111–406
Low density lipoprotein cholesterol (mg/dL)	143.3	±46.30	65–329
Triglycerides (mg/dL)	163.6	±96.00	57–595*
High density lipoprotein cholesterol (mg/dL)	44.7	±13.3	9–81*
Ratio $= \frac{\text{total cholesterol}}{\text{high density lipoprotein cholesterol}}$	5.5	±3.2	2.3–29.7*

* Includes one case with extreme values: HDL cholesterol = 9, Triglycerides = 595, Ratio of total cholesterol/HDL cholesterol = 29.7.

to the history of a cerebrovascular accident or transient ischemic attack, or both is also examined within each cardiac subgroup.[5]

Trends of serum lipids with advancing age were determined by regression analysis, and the slopes of the lines were tested for statistical significance with the Students' tests.[5]

Since the triglyceride values were not distributed normally, a log transformation of the values was used for the calculation of correlations and significance testing.

All the tests were declared significant at the 5% probability level. Since a number of tests were done, some results may be expected to be significant by chance alone.

RESULTS

The mean values, standard deviations and ranges for age and serum lipids for the group as a whole are shown in Table I and those of the subgroups by cardiac status in Table II.

There are no statistically significant differences between the subgroups except for HDL cholesterol which is borderline, $P = .06$. This reflects the lower mean value of 40.8 mg/dL in the group with clinical coronary artery disease compared to that of 48.5 mg/dL and 45.6 mg/dL in the other subgroups.

There was a statistically significant decrease in total and LDL cholesterol at successively advancing ages in the total group, $P = .01$ (Fig 1). The triglycerides and the ratio of total cholesterol to HDL cholesterol manifest a slight decrease with advancing age (Fig 2). Two of the three groups had significant decreases in mean lipid values. Among those subjects with clinical coronary heart disease there is a negative correlation at successively advancing ages with values of total cholesterol and log triglycerides, $P = .05$ (Table III). In those subjects with no clinical evidence of heart disease there is a negative correlation, $P = .01$, with total and LDL cholesterol. In the third group with other forms of heart disease, there were no significant correlations with any of the serum lipid levels (Table III).

When the mean lipid values of those subjects with and without a prior history of cerebrovascular accidents or transient ischemic attacks were compared, there were no significant differences. However, all of the values except HDL cholesterol were higher in the group with cerebrovascular disease.

The correlation of prior cerebrovascular accident or transient ischemic attack with lipid values revealed significant correlations only in the coronary heart disease group. This group had significantly higher levels of total cholesterol, LDL cholesterol and log triglyceride levels.

DISCUSSION

A comparison of these results with other groups of women in a comparable age group reveals similar mean values for total and LDL cholesterol. Our group had a higher mean value for triglycerides and a lower mean value for HDL cholesterol.[1,6–9] As a consequence the ratio of total cholesterol divided by HDL cholesterol was higher in our group.

The statistically significant decrease in total and LDL cholesterol values of individuals of successively advancing age is similar to the findings of Nicholson et al[1] in a group of subjects over 80 years of age. This may be a reflection of selective mortality—the progressively greater loss of individuals with an unfavorable risk factor for coronary heart disease in a cohort of individuals of the same age followed over a period of time. However, these findings may be due to other factors that affect serum lipid levels, such as nutrition, diabetes, diuretic agents and other drugs, smoking activity, and alcohol consumption.

The subgroups by cardiac status show no statistically significant differences in mean lipid values or the ratio of total cholesterol to HDL cholesterol. However, the higher mean values for triglycerides and the ratio of total cholesterol to HDL cholesterol and the lower mean value of HDL cholesterol in the subgroup with clinical coronary heart disease, $P = 0.06$, may be of some predictive value. Williams, Robinson and Bailey[10] in a study of 2,568 men in England found no significant relationship between HDL cholesterol level or the ratio of total cholesterol to HDL cholesterol and electrocardiographic or chest film abnormalities.

The lack of significant differences between the subgroups may be due to the appreciable incidence in the aged of coronary heart disease detectable only by cinecoronary angiography, stress testing with radionuclide ventriculog-

TABLE II. Mean Lipid Values by Cardiac Status (N = 100)

	Coronary Heart Disease (N = 37)		Other Heart Disease (N = 29)		No Clinical Heart Disease (N = 34)		
	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	Group Comparisons
Age (years)	86.7	±10.4	83.9	±9.3	82.5	±11.8	NS
Total cholesterol (mg/dL)	221.9	±61.1	211.0	±42.4	224.1	±54.8	NS
Low density lipoprotein cholesterol (mg/dL)	143.6	±51.1	135.9	±40.0	149.3	± 46.2	NS
Triglycerides (mg/dL)	192.8	±127.1	146.8	±57.9	146.3	±75.1	NS
High density lipoprotein cholesterol (mg/dL)	40.8	±11.5	48.5	±14.1	45.6	±13.7	.06*
Ratio $= \frac{\text{total cholesterol}}{\text{high density lipoprotein cholesterol}}$	6.4	±4.8	4.7	±1.4	5.2	±1.6	NS

* Borderline signficance
NS, not significant

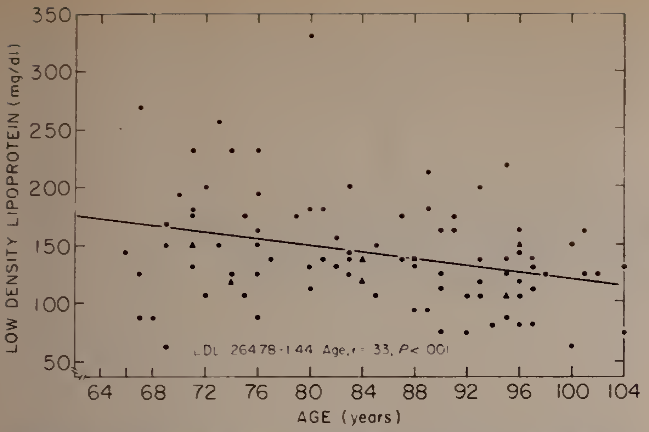

FIGURE 1. Relationship between age and low density lipoprotein cholesterol determinations. (● = 1 observation, ▲ = 2 observations, ■ = 3 observations.)

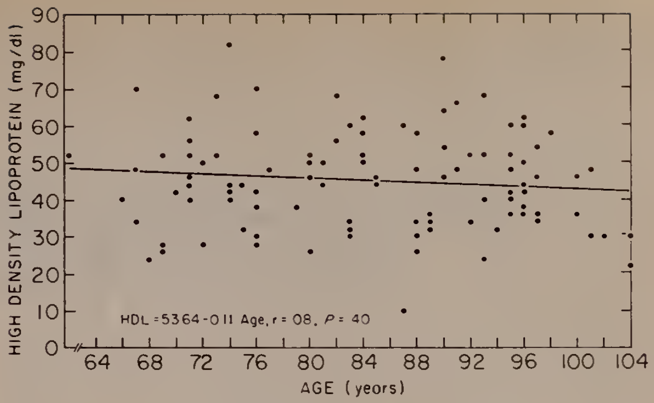

FIGURE 2. Relationship between age and high density lipoprotein cholesterol determinations.

raphy, thallium scintography, or at post mortem examination.

We did not find the striking decrease in HDL cholesterol levels found among younger individuals with prior strokes reported by Nubiola et al[2] and Rossner et al.[3] The statistically significant positive correlations between elevations of total and LDL cholesterol and log triglycerides and prior cerebrovascular disease in the subgroup with clinical coronary heart disease is consistent with the strong relationship between coronary and cerebrovascular disease noted in the Framingham study.[11] Whisnant et al[12] and Goldner et al[13] have reported that the leading cause of death among those with transient ischemic attacks is cardiac disease, most often acute myocardial infarction.

Acknowledgment. Ms Judith Gideon, Laboratory Supervisor, assisted in the performance and coordination of the results of the laboratory determinations, and Ms Joan Lindower assisted in the analysis of the weight status of the series.

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TABLE III. Correlation of Lipid Values with Age and by Cardiac Status (N = 100)

	Total Cholesterol	Log Triglycerides	High Density Lipoprotein Cholesterol	Low Density Lipoprotein Cholesterol	Ratio of Total Cholesterol to HDL Cholesterol
Total group (N = 100)					
Age (Years)	−0.34*	NS	NS	−0.33*	NS
By cardiac status					
Coronary heart disease (N = 37)	−0.36*	−0.42**	NS	NS	NS
Other heart disease (N = 29)	NS	NS	NS	NS	NS
No clinical heart disease (N = 34)	−0.46*	NS	NS	−0.49*	NS

* Statistically significant p < .01
** Statistically significant p <.05
NS Not significant

A 77-year-old man with recurrent hemiparesis, cardiac arrhythmias, and angina pectoris

CASE PRESENTATION

Peter L. Arquin, MD (Attending Cardiologist): A man was admitted for the first time in 1967, at age 61 years, with the sudden onset of left-sided weakness that was transient yet recurrent. He presented in the Emergency Department with a significant left hemiparesis. He had a 30 pack-year history of cigarette smoking; he was obese and, at the time of admission, hypertensive. He was known to have a postprandial serum glucose level of 195 mg/dL. His admission in 1967 was characterized by neurologic symptoms and signs that resolved over several days after heparin therapy was initiated; the therapy was continued for four weeks. He was also treated with a combination of 95% oxygen and 5% carbon dioxide. He had one recurrence of neurologic symptoms during anticoagulant therapy. He was discharged on coumadin.

Two months later the patient was readmitted for an aortic arch study because of persistent mild left-sided weakness. The study was reported as being within normal limits.

The patient was asymptomatic until 1968, when he had an acute thrombosis of the left saphenous vein. Initial conservative therapy was followed by vein stripping of the greater saphenous system. He had no further evidence of thromboses, despite discontinuing anticoagulant therapy; up to 1974 his blood pressure in that interval ranged from 140 to 170 mm Hg systolic, and 80 to 95 mm Hg diastolic. In 1974 he began to experience angina pectoris, for which he was treated with sublingual nitroglycerine as needed. In 1976 his blood pressure was recorded as 170/80 mm Hg and an electrocardiogram revealed atrial and ventricular ectopy and first-degree atrioventricular heart block. He complained about an uncomfortable sensation in his chest when trying to sleep on his left side. Physical examination at that time demonstrated an S_4 gallop; his blood pressure was mildly elevated.

In 1981 he was readmitted with recurrent weakness in the left arm, with transient hemiparesis that resolved rapidly. A computerized tomographic scan of the head was within normal limits, and he was treated with aspirin for a presumed transient ischemic attack. In 1982 he was again admitted, this time with atrial fibrillation and congestive heart failure, complicated by a pneumonia in the lower lobe of the left lung. Treatment consisted of digoxin, diuretics, and antibiotics, with resolution of the complications.

The patient's final admission was due to symptoms of unstable angina pectoris. Therapy with low-dose isosorbide dinitrate, 5 mg four times per day, was begun; because of the persistence of pain, the sublingual preparation was substituted on a more frequent basis, together with nitroglycerine paste. One episode of angina was terminated by sublingual nifedipine. Two days after admission, a recurrence of angina persisted for approximately six hours; the patient was given nitroglycerine by intravenous drip and nifedipine three times daily. An electrocardiogram suggested changes associated with an acute inferior myocardial infarction.

Approximately three days after admission the patient began to have brief episodes of shortness of breath for 15 to 30 minutes, with abrupt increases of respiratory rate from 20 to 40/min. An arterial blood gas study during this period revealed a Po_2 of 56 mm Hg on two liters of oxygen. He was treated with 5,000 units of heparin subcutaneously twice daily. Two days before death he experienced premonitions of death. He began to have respirophasic chest pain, but no pericardial rub was heard at that time. Intravenous nitroglycerine and indomethacin therapy was restarted. His pain subsided, and on the fifth hospital day the cardiologist recommended discontinuing the nifedipine. An echocardiogram was performed to determine the presence of a pericardial effusion. On the following (sixth hospital) day, while straining at stool, the patient had a cardiac arrest with persistent electromechanical dissociation, and he did not respond to attempts at resuscitation. Two pericardiocenteses did not reveal any pericardial fluid.

Vittal B. Chanamolu, MD (Attending Radiologist): The angiogram obtained in 1967 outlined the aortic arch and the neck vessels. An ulcerated intimal plaque was evident in the left carotid artery, just above the bifurcation. The rest of the great vessels of the neck were patent and otherwise appeared unremarkable. In 1981 the CT scan of the head was within normal limits. On admission in April 1982, the preliminary chest film showed no acute changes in the lung fields; there was scarring in the left mid-lung field, as well as chronic pleural changes at the base of the left lung. Mild cardiomegaly was present; the pulmonary vascularity was within normal limits. However, on the final admission, the patient's chest film demonstrated bibasilar infiltrates, a left

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Based on the clinicopathologic conference (CPC) held at Mary Imogene Bassett Hospital, Cooperstown, New York, July 28, 1983.

Moderator: Harlan D. Alpern, MD, Pathologist-in-Chief.

Clinical Discussion: Peter L. Arquin, MD, Attending Cardiologist.

Pathology Presentation: Dr Alpern.

Editor: JOHN T. FLYNN, MD.

Address correspondence to Dr Flynn, Consulting Editor, *New York State Journal of Medicine*, PO Box 5404, 420 Lakeville Rd, Lake Success, NY 11042.

pleural effusion, and distended central pulmonary vessels, and was indicative of cardiac failure. On subsequent films, there appeared to be partial clearing of the infiltrates, although the left pleural effusion had increased in amount.

Dr Arquin: Dr Whelan, will you comment on the patient's neurologic problems? We will then address the cardiac problems.

Mary Anne Whelan, MD (Attending Neurologist): This patient's history of transient ischemic attacks 20 years before his death illustrated several points about the extent and limitations of our knowledge concerning this problem. The first and most obvious point, made by Dr Arquin, is that three major risk factors were present, not only for transient ischemic attacks but also for cardiovascular disease in general—a history of smoking, hypertension and hyperglycemia.

It is quite possible that this patient's original neurologic symptoms were never entirely resolved. He presented with numbness and weakness of the left side of the face, left arm and left leg, together with dysarthria and an extensor plantar response on the left. Review of his hospital record indicates that on the following day he had four similar attacks, all stereotyped in the same fashion, lasting perhaps five to 10 minutes. Our neurosurgeon, Dr Mackie, elicited a history of nominal aphasia that the patient had had for about one month preceding these episodes of transient ischemic attacks. Each aphasic episode lasted about 30 to 40 seconds, during which the patient could not get out the word that he wanted. Dr Mackie found persistent left visual extinction on double simultaneous stimulation of the visual fields.

The patient's constellation of symptoms placed his area of risk in the right carotid territory. The left-sided weakness in itself was not very specific; when a dysarthria and a nominal aphasia are added, the lesion can be placed more specifically in the right carotid and in particular in the right middle cerebral territory, bearing in mind that the patient was ambidextrous and may have had right-sided dominance for language. The patient's tendency to visual extinction might be attributed to a parietal neglect phenomenon rather than to a more posterior area.

He was treated, as was fashionable at the time, with a rational therapy—oxygen and carbon dioxide, the idea being to improve cerebral blood flow. He was also treated with anticoagulation medication. We have discarded the first method of treatment, by and large, but not the second.

The patient did not experience difficulty until nearly 15 years later. This long interval highlights a second puzzling aspect of transient ischemic attacks, namely, the tendency to stereotyped recurrence in what appears to be very much the same vascular territory that was previously affected. If the vascular territory is large—the entire middle cerebral artery distribution—then one can hypothesize the presence of emboli that lodge recurrently in that major distribution. But if much smaller branches in that distribution appear to be obstructed intermittently, then it is very difficult to imagine that embolic material is striking at exactly the same territory each time. Recurrent emboli may predispose a typical watershed area to blockage of flow by lodging further down, then subsequently fragmenting and moving on.

In any case, the patient illustrated the final points, of which we are certain, in the natural history of transient ischemic attacks. First, the patient certainly is at risk for stroke in the future; the exact figures are much disputed, but some reports indicate that as many as one third of these patients will have a stroke within five years. But secondly, and of even greater importance, the risks for cardiac morbidity and mortality are generally considered to be 3 to 10 times the risks of cerebral vascular morbidity and mortality.

Robert Sioussat, MD (Attending Physician): Let me say a word about the older form of treatment of transient ischemic attacks with 95% oxygen and 5% carbon dioxide. That very interesting mode of treatment was based on the theory that the carbon dioxide would produce cerebral vasodilatation, which indeed it does, and that the high oxygen level would then provide a good oxygen flow to the brain, which it did. The only problem was that when cerebral flow studies were made available, it was discovered that the area of ischemia and infarction had lost its autoregulation. The consequences were that the normal vessels were dilated, and they diverted blood flow away from the involved area. The technique had to be abandoned, but it is worth mentioning as another example of therapeutic considerations that made sense at the time but made much less sense as physiologic research continued.

Dr Arquin: I would like to review the electrocardiograms at this time. The patient's first electrocardiogram, taken in 1967 when he was admitted with the transient ischemic attacks, showed no abnormalities. In 1976, his electrocardiograms reflected the onset of first-degree atrioventricular block, apparently not related to drug toxicity. Significant ventricular and atrial ectopy were also evident, even in the single 12-lead electrocardiogram. This would make us suspect a considerable degree of unobserved irregular rhythm at other times. The patient was asymptomatic in this regard however.

The electrocardiograms at the time of his admission with atrial fibrillation indicated that his rhythm shifted back and forth from normal sinus to atrial fibrillation until the latter arrhythmia persisted.

At the time of the second admission for his neurologic problems, the electrocardiogram showed a very chaotic atrial rhythm, with frequent and multifocal premature atrial contractions; there was no evidence of an ischemic event. However the patient did have a significant amount of ventricular ectopy, probably with premature ventricular contraction couplets.

Eventually the electrocardiogram showed atrial fibrillation on a more permanent basis. One is tempted to suspect atrial flutter because of the coarseness of the atrial fibrillatory waves. However, I prefer to make the diagnosis of atrial flutter on the basis of the typical saw-toothed pattern in the inferior leads, so I think this electrocardiogram demonstrated fairly typical atrial fibrillation with a rapid ventricular rate.

On the patient's final admission with unstable angina, the electrocardiogram demonstrated ST segments compatible with ischemia, with significant ST elevation in standard lead III. Although seemingly not very impressive, this elevation of the ST segment should be compared to the total QRS height; as a percentage of QRS height, this then becomes a significant amount of ST segment elevation.

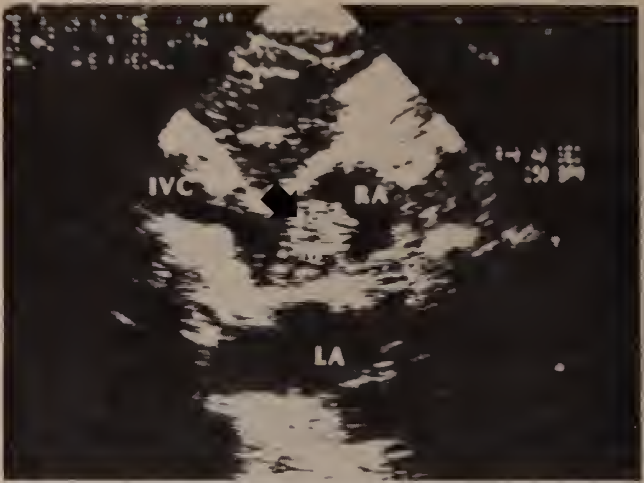

FIGURE 1. 2-D echocardiogram showing mass within right auricle (arrow). IVC, inferior vena cava; RA, right auricle; LA, left auricle; M, mass.

There were also reciprocal ST segment changes in the lateral and precordial leads.

There have been suggestions in the medical literature during the past year that what used to be thought of as benign reciprocal ST segment changes may, in fact, represent significant ischemia in an additional coronary bed. In this patient's case, the left coronary system, rather than the right coronary system alone, would thus be involved.

On the second hospital day, on follow-up electrocardiogram, the ST segment elevation in standard lead III had disappeared and there were T wave inversions, which are compatible with evolution of an infarction or resolution of transient ischemia. The patient still presented nonspecific changes in the precordial leads.

On the third hospital day, marked by the six hours of unrelieved angina, the electrocardiogram suggested that the patient was in the throes of an inferior myocardial infarction. The patient was sustaining an infarction of the diaphragmatic region of the heart, and the changes observed were similar to those previously evident in the lateral precordial leads.

With the recurrence of his discomfort, the electrocardiogram showed continued elevation of the ST segments that may have been less elevated in the interval since the last electrocardiogram, or may simply reflect the slow resolution of such elevations.

With another episode of pain, the ST segments were again elevated, and a broadening of the R wave in these leads was becoming evident. Although these changes are not diagnostic for posterior extension of the infarct, we would be concerned about such a possibility in relation to this patient's diaphragmatic infarct. This process has been referred to not as an extension, but rather as an expansion of the area of infarction. In lead V 1, the R wave is now much taller than previously noted, and this would be compatible not only with an inferior diaphragmatic infarct, but also with posterior extension of the infarction. The clinical situation was not improving but actually deteriorating.

At this point I would like to review the 2-D echocardiogram that was performed the day before death (Fig 1). The subxiphoid echocardiogram showed the liver, the inferior vena cava entering the right atrium, the left atrium, and a portion of the pulmonary veins. In the right atrium there was a large structure located on the atrial septum; on the video playback there appeared to be motion during systole that suggested attachment by a pedicle to the septum, rather than by direct fixation to the atrial wall. The differentiation between an atrial myxoma and an intra-atrial clot is difficult. A highly mobile structure on a pedicle that flops across the tricuspid valve or the mitral valve during diastole offers strong evidence that it is a myxoma. However, when the structure is not moving so obviously, the distinction between myxoma and thrombus is more difficult. Thus, the detection of motion is extremely important. The texture of echographic representations of such masses may have importance; some experts report that a thrombus may present a layered appearance and that a myxoma would tend to be more homogeneous. But differentiation on this basis breaks down in actual practice. A major reason for this discrepancy is the extreme rarity of atrial myxomas. They occur in one of 10,000 autopsies, so that there is no sufficiently large series of cases to permit clear definition of echocardiographic criteria.

In general, right atrial myxomas are much less frequent than those in the left atrium; usually with a right atrial myxoma, there is a left atrial myxoma as well.

David Vaules, MD (Attending Cardiologist): I read it as a clot.

Dr Arquin: David read it as a clot, but for the sake of argument, I bring up the difficulties that we encounter in discriminating between a clot and a myxoma.

Donald Lewis, MD (Attending Physician): Was the mass seen on any of the other four-chamber views of the echocardiogram?

Dr Arquin: No, it was not, but these were rather difficult views to obtain. This was a difficult patient on whom to get a good echocardiogram, so that the standard long-axis, short-axis and parasternal views and the apical views were not of sufficiently good quality for diagnostic purposes. The subxiphoid view, however, was of good quality and was the only one on which we saw this structure properly in the right atrium.

In summary, then, we have a hypertensive, obese man with a significant history of cigarette smoking, longstanding angina—recently of the unstable variety—and cardiac arrhythmias who suffered a myocardial infarction, despite standard therapy for unstable angina. During the last four days of his life he had recurrent chest pain, and unexplained dyspnea and hypoxia. I believe that the findings of the pathologist will prove to be diffuse arteriosclerotic cardiovascular and cerebral vascular disease, complicated by an acute inferoposterior myocardial infarction. His sudden death points to cardiac rupture or dissection of an intramyocardial hematoma. I believe that pulmonary emboli will be found as the explanation for the recurrent hypoxia, although that could be explained by the congestive heart failure. The question of the atrial mass is a difficult one to answer, but I believe there is a good chance that it is a right atrial myxoma. The reason for death was most probably rupture of the left ventricle, since it occurred about the time that such a catastrophe is likely to happen.

James Walker, MD (Medical Resident): Would you comment on the steadily decreasing height of the QRS

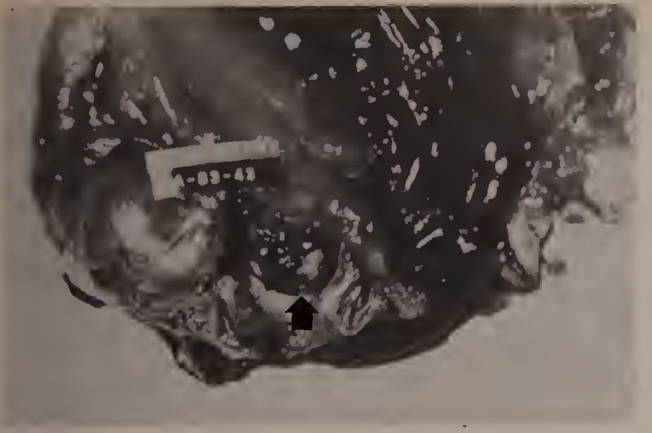

FIGURE 2. Clotted blood (at right) within pericardial sac; mass within right auricle (arrow).

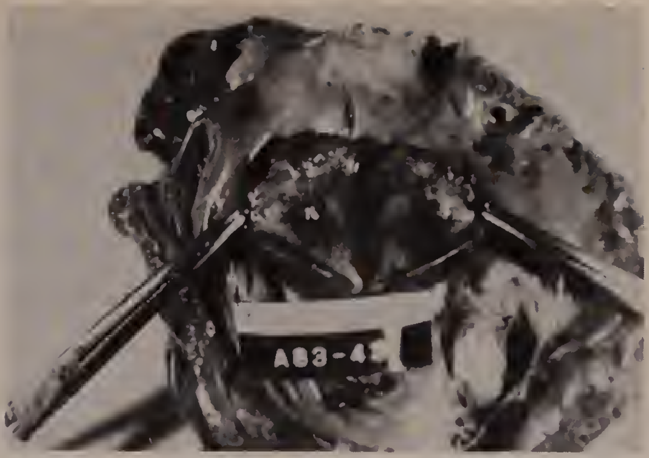

FIGURE 3. 4-cm right atrial myxoma (bisected) attached to atrial septum.

complexes during the course of the hospitalization?

Dr Arquin: I would think it a relatively nonspecific finding, since it occurred only in the limb leads and not in the precordial leads. It certainly can represent a pericardial effusion, although that was not seen on the echocardiogram; the recording was clear enough for us to say that this patient did not have a major pericardial effusion.

CLINICAL DIAGNOSES

Diffuse atherosclerotic cardiovascular and cerebrovascular disease.

Transient ischemic attacks, secondary to diagnosis above.

Coronary artery atherosclerosis, with unstable angina pectoris, atrial and ventricular arrhythmias, posterior-inferior myocardial infarction, and terminal rupture of the left ventricle.

Right atrial mass, most probably a myxoma.

PATHOLOGY PRESENTATION

Harlan D. Alpern, MD (Pathologist-in-Chief): The immediate cause of death was hemopericardium as a result of a ruptured acute myocardial infarction. At autopsy, the pericardial sac was distended, tense, and contained 300 mL of dark purple, clotted blood (Fig 2). The acute myocardial infarction was transmural and involved the posterior inferior portions of the left ventricle; the tract of rupture was easily demonstrated between the left ventricular lumen and the pericardial sac.[1,2]

The tract was lined by necrotic myocardium. There was coagulative necrosis of the myofibers that were homogeneous and amorphous, with loss of cross striations and of nuclei. There was a dense inflammatory infiltrate between the necrotic myofibers, which was dominated by neutrophils. Along the surface of the visceral pericardium was a fibrinopurulent exudate, which is commonly seen in transmural myocardial infarcts. The infarct was histologically compatible with one of about four days of age.

The heart mass was 400 g, which is a moderate increase above normal. There was three-vessel coronary atherosclerosis which was severe; in addition there was a thrombus in the left circumflex branch. There was evidence of old ischemic heart disease—not of a remote discrete infarct but of multifocal chronic ischemic myocardial fibrosis, demonstrated by trichrome stain that identified collagen laid down to replace lost myofibers.

In the right atrium there was a mass approximately 4 cm in diameter, with a short pedicle at its site of attachment to the septal wall. On cut section, the mass was orange-tan and dark red, soft and somewhat gelatinous (Fig 3). The whole mount demonstrated mucoid material, cellular elements, and blood within the mass. Microscopic examination revealed that this mass was a myxoma, composed of spindle-shaped and polygonal cells lying in an acid-mucopolysaccharide stroma, and containing numerous blood vessels (Figs 4, 5).

The myxoma is the most common primary tumor of the heart.[3–5] It is most often found in the left atrium, less commonly in the right atrium, and on rare instances in the ventricles. It is believed to be derived from a totipotential primitive mesenchymal cell that lies beneath the endocardial surface and is productive of acid mucopolysaccharide, of vessels within the mass, and of other fibers such as those composed of collagen or reticulum. The electron micrograph demonstrated a typical cell of a myxoma; the nuclear-cytoplasmic ratio was in the moderate range, and there were numerous dark granules in the cytoplasm, most of which were lysosomes. The appearance on the electron micrograph was that of a primitive mesenchymal cell.

A tissue section stained by the alcian blue technique demonstrated acid mucopolysaccharide in the stroma of the tumor, produced by the cells of the myxoma.

In some areas of the myxoma, there were numerous small blood vessels, with plump endothelial cells and numerous plasma cells. In some myxomas, hematopoietic tissue may appear. A reticulin stain demonstrated reticulin in relation to some of the larger vessels in the myxoma; elastic fibers were also found together with deposits of iron.

In the Armed Forces Institute of Pathology series of 138 cardiac myxomas in 130 patients, 74.5% were found in the left atrium, and 18.1% in the right atrium.[6] Myxomas also occur in locations other than the heart, including soft tissues and the upper respiratory tract.

An incidental and unrelated finding at autopsy in this patient was the presence of a tumor mass in the right temporal fossa, seen when the brain was removed. The tumor

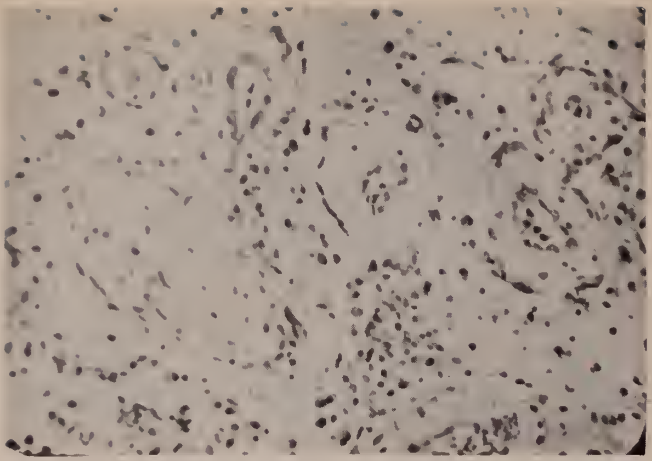

FIGURE 4. Photomicrograph of myxoma showing spindle-shaped and polygonal benign mesenchymal cells, small blood vessels, and plasma cells in myxoid stroma. Hematoxylin and eosin stain; original magnification ×40.

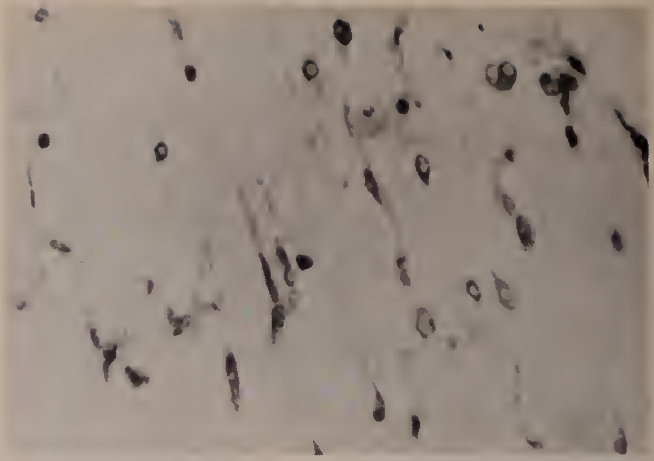

FIGURE 5. Hypocellular area of myxoma with ground mesenchymal cells in myxoid stroma. Hematoxylin and eosin stain; original magnification ×100.

was smooth, pink, measured 4 cm in maximum dimension, and proved to be a meningioma. Microscopic examination indicated the presence of whorling elements consisting of fibroblastic cells; psammoma bodies were found, representing calcifications that are typical of meningiomas. The tumor had not invaded the dura or the bone.

A more interesting incidental neurologic finding was the presence of a congenital saccular aneurysm that measured 4 mm in diameter. This so-called berry aneurysm was located in the middle cerebral artery near the origins of the anterior cerebral artery branch and the posterior communicating artery. Congenital saccular aneurysms are thought to occur as the result of hypoplasia of the muscularis of the artery and of its internal elastic lamina; they are infrequently seen at autopsy in the nonruptured state. The best series that gives some indication of this rarity was reported early in this century during the presurgical era, from the London Hospital in England. In the period 1908–1913, in a series of 4,347 autopsies, the incidence of asymptomatic incidental berry aneurysms was 0.64%—approximately one in 160 people have unsuspected berry aneurysms. The berry aneurysm in this case is the first seen here in many years in the unsuspected, unruptured state. Rupture occurs most commonly in the fifth decade of life.

The Gomori trichrome whole-mount demonstrates that the aneurysmal sac is composed almost exclusively of fibrous connective tissue. The elastic lamina and the muscularis are hypoplastic and in some areas aplastic. Pea-size aneurysms are most typical, but such aneurysms can vary from the size of a head of a pin up to the largest reported, which was 30 mm in diameter.

The remainder of the autopsy revealed marked generalized and cerebrovascular atherosclerosis; the carotid arteries were approximately 80% occluded by arteriosclerotic plaques that I believe were largely responsible for the patient's transient ischemic attacks. In the right occipital lobe there was a laminar cortical infarct measuring 3.5 cm in diameter. Based on histologic analysis, the age of this infarct was probably in the range of six months to a year. Its center contained hemosiderin-laden macrophages and along the margins were numerous gemistocytic astrocytes that had produced a glial scar. There were no pulmonary emboli and no significant intrinsic disease of the kidneys, including glomerulosclerosis, diabetic or otherwise.

An additional unsuspected finding was a duodenal ulcer that measured 2 cm in diameter and was without significant hemorrhage. An abdominal aortic aneurysm, 5 cm in diameter, was present in the infrarenal region secondary to atherosclerosis. There were emboli of cholesterol in the renal arteries, producing cholesterol clefts with giant-cell reaction in the renal vessels.

In summary, this man died in electromechanical dissociation due to massive hemopericardium, as the result of the perforation of an acute myocardial infarct involving the posterior and inferior walls. He had generalized atherosclerosis involving the aorta, the coronary arteries, and the carotid arteries; he had the unusual findings of a right atrial myxoma and an unruptured saccular intracranial aneurysm. In addition, a duodenal ulcer, a meningioma, and an abdominal aortic aneurysm were found.

FINAL DIAGNOSES

Hemopericardium secondary to posterior wall rupture with acute transmural posterior myocardial infarction.

Marked three-vessel coronary atherosclerosis with recent thrombosis of the left circumflex artery.

Myxoma of the right atrium.

Meningioma of the right temporal fossa.

Old cortical laminar infarct of the right occipital cortex.

Saccular aneurysm (4 mm) of the right middle cerebral artery trifurcation, unruptured.

Severe ulcerative atherosclerosis of abdominal aorta, with small infrarenal aortic aneurysm.

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The familial incidence of mitral valve prolapse

A report of three generations in one family

ELMER PADER, MD

Mitral valve prolapse (MVP), a common and usually benign condition, occurs in from 4 to 10% of the adult population.[1-5] The possibility of a familial incidence of this condition, first recognized in 1964 on the basis of similar auscultatory findings in several members of a family,[6] was later confirmed in other studies.[7,8] With the advent of echocardiography the presence of MVP, even in the absence of the characteristic systolic click and murmur, could be demonstrated. This enabled the study of large series of such patients and their families. These studies have confirmed the high frequency of MVP among relatives, and they suggest that the condition is inherited in an autosomal dominant fashion.[9-12]

This report describes a family with MVP, established by the presence of the characteristic mid-systolic click and confirmed by M-mode echocardiography, in three successive generations—grandmother, mother and daughter. It demonstrates that MVP may be asymptomatic and compatible with longevity. One previous report,[6] based on similar auscultatory findings but without echocardiographic confirmation, described MVP in a grandmother, mother and daughter.

CASE REPORTS

Patient 1. This patient was a 34-year-old white woman with a medical history that revealed no major illness or surgery. She presented with a respiratory infection, and upon examination a mid-systolic click was detected. She denied palpitations, chest pain or syncope and was never told of a heart murmur. Positive physical findings were confined to the heart. Auscultation revealed a mid-systolic click and a grade II/VI mid- to late systolic murmur at the apex and lower left sternal border that were best heard in the upright position. There were no skeletal or connective tissue abnormalities. A chest roentgenogram and electrocardiogram did not disclose any abnormalities. M-mode echocardiography (Fig 1) revealed late-systolic MVP.

Patient 2. The mother of Patient 1 was a 57-year-old white woman. Her medical history included only mild hypertension. She had noted "palpitations" intermittently, but an arrhythmia was never documented. She denied chest pain, syncope or prior knowledge of cardiac abnormalities. Examination during a routine check-up revealed a blood pressure of 130/90 mm Hg, a mid-systolic click and a grade II/VI late systolic murmur. The remainder of the examination was within normal limits, and there were no skeletal or connective tissue abnormalities. A chest roentgenogram and electrocardiogram disclosed no abnormalities. An M-mode echocardiogram (Fig 2) revealed late systolic mitral valve prolapse.

Patient 3. The mother of Patient 2 and the maternal grandmother of Patient 1 was a 78-year-old woman who complained of occasional lightheadedness and rare, unsustained palpitations. Her history included a benign hepatic cyst, first detected seven years previously, and mild hypothyroidism for which she was receiving replacement therapy. She had never been told of abnormal cardiac findings, and there was no history of chest pain or syncope. Physical examination revealed a mid-systolic click and a grade I/VI late systolic murmur at the apex. There was a slight pectus excavatum deformity, and the liver was palpable three finger breadths below the xiphoid. She was euthyroid on clinical and chemical evaluation. The findings of a chest roentgenogram and electrocardiogram were normal. An M-mode echocardiogram (Fig 3) disclosed late-systolic mitral valve prolapse.

DISCUSSION

Careful auscultation of the heart with an awareness of the significance of non-ejection clicks and late systolic murmurs, together with the advent of echocardiography, have led to the detection of MVP in asymptomatic patients and have demonstrated that it is a common abnormality. Brown et al[3] screened a population of 520 women without a history of heart disease and found MVP in 6% of them. In a series of 100 young women, MVP was detected by echocardiogram or phonocardiogram in 10%.[2] Of 1,169 healthy women, 74 (6.3%) were found to have MVP on auscultation, and in 60 of these 74 patients the echocardiogram confirmed the diagnosis.[5]

The incidence of MVP has been considered to be higher in women than men. However, an echocardiographic study of 100 randomly selected asymptomatic young men disclosed four with MVP, none of whom had the characteristic click-murmur.[1] In another study, M-mode and 2-D echocardiograms were performed in 1,058 subjects, and MVP was found in 3% of the men and 4% of the women.[4]

Reports of a familial incidence of MVP appeared soon after the syndrome was first described. Barlow and Bosman[6] studied 19 relatives of six patients with MVP. They found one instance in which a mother and son were affected, and one instance in which grandmother, mother and daughter were affected. The diagnosis of MVP was established by physical findings alone. Stannard et al,[7] in a study of 13 patients with clicks and late systolic murmurs, found similar auscultatory findings among three sisters in one family and two sisters in another family.

Shell et al[8] first proposed an autosomal dominant mode of inheritance in a report of similar physical and phonocardiographic findings in 23 family members of four index cases. The advent of echocardiography facilitated the detection of MVP in patients and their

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From the Division of Cardiology, Department of Medicine, Mount Sinai School of Medicine, City University of New York, NY.

Address correspondence to Dr Pader, 1070 Park Ave, New York, NY 10128.

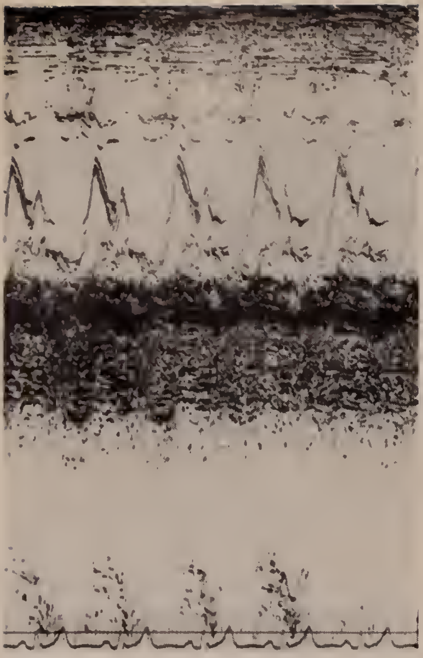

FIGURE 1. M-mode echocardiogram of Patient 1 showing late systolic mitral valve prolapse.

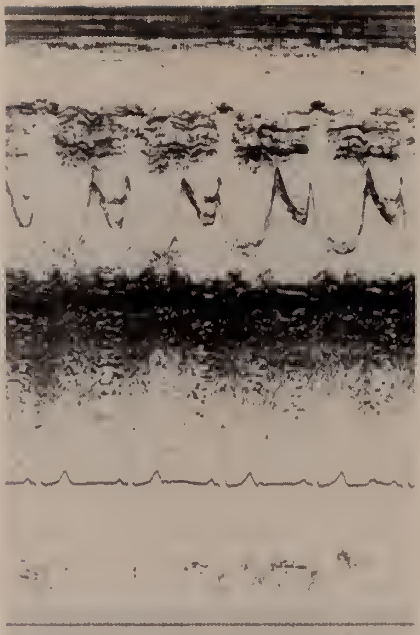

FIGURE 2. M-mode echocardiogram of Patient 2 showing late systolic mitral valve prolapse.

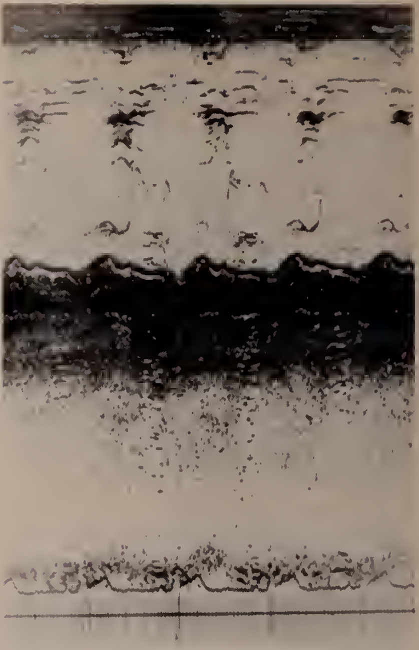

FIGURE 3. M-mode echocardiogram of Patient 3 showing late systolic mitral valve prolapse.

relatives. Weiss et al[12] studied 17 index cases and 57 of their first-degree relatives by echocardiography. Twenty-seven of the 57 relatives had MVP, with transmission to both sexes but primarily to female subjects.

The concept of an autosomal dominant transmission is supported by several additional studies. Seventy-three relatives, 30 male and 43 female, of 12 patients with MVP were studied[10]; 13 of the male relatives and 20 of the female relatives were affected. Takeda et al[11] compared the phonocardiograms and echocardiograms of 62 first-degree relatives of patients with MVP with those of 30 controls. A click or murmur was found in 9% of the relatives of patients with MVP, but none was found in the control group. Evidence of MVP in relatives occurred in 38% of families of patients with the syndrome. Devereux[9] studied 45 patients with MVP and 179 of their first-degree relatives. Echocardiographic evidence of MVP was found in 54 of the 179 relatives: 37 of 90 female relatives and 17 of 89 male relatives. In 23 families, members of two generations were affected. The inheritance of the condition was unrelated to the severity of the disease or to the presence or absence of symptoms in the proband, and both symptomatic and asymptomatic cases were detected in relatives. The Framingham study[4] disclosed evidence of MVP in 9% of offspring of subjects with MVP, with 4 times as many cases appearing in female offspring as in male offspring.

The present report of MVP in one family, with similar physical and echocardiographic findings in three successive generations of female members, confirms the familial occurrence of this condition and the sex-dependent mode of expression.

MVP is the most prevalent inherited cardiac abnormality. Its prevalence in individual subjects and in families may be underestimated because of the silent or asymptomatic nature of the condition in most people. Symptoms such as palpitations, chest pain, syncope or dyspnea do occur in some patients, however. In a much smaller number of affected subjects four major complications—sudden death, infective endocarditis, spontaneous chordal rupture, or progressive mitral regurgitation—may occur. It seems advisable to identify patients with MVP as early as possible. Because of the strong familial tendency, all first-degree relatives should also be screened by careful auscultation or echocardiography, or both.

Acknowledgment. Ms Phyllis W. Ryan assisted in the preparation of the manuscript.

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Massive colonic hemorrhage secondary to infection with *Strongyloides stercoralis*

SALVATORE DELLACONA, MD, NATHANIEL SPIER, MD, ZELMA WESSELY, MD, IRVING B. MARGOLIS, MD

Although millions of people worldwide are infected with *Strongyloides stercoralis*, the majority of infections are asymptomatic or evoke minimal reaction. Exsanguinating hemorrhage is an unusual manifestation of colitis regardless of the cause of the disease; its occurrence secondary to strongyloides infection is rare. The recent successful treatment of a patient for massive hemorrhage secondary to strongyloides infection of the colon prompted a review of the literature that revealed only three other cases with massive hemorrhage and the roentgenographic and pathologic changes of strongyloidiasis, only one of whom survived.

CASE REPORT

A 42-year-old woman was admitted to the emergency room of the Queens Hospital Center with a 12-hour history of rectal bleeding. Her vital signs were stable, and she was in no apparent distress. There was a 20-year history of strongyloidiasis. She had had five previous episodes of bleeding and had, on several occasions, been treated with thiabendazole, both in the United States and in Jamaica. There was no history of pulmonary complaints.

Shortly after being admitted to the surgical intensive care unit for observation and further studies, she began to complain of cramping abdominal pain. This was soon followed by the passage of a large amount of bright red blood via the rectum. Sigmoidoscopy showed a normal rectal mucosa with the blood coming from above 25 cm. She became hypotensive and diaphoretic and was treated with volume replacement, including 12 units of packed cells, crystalloids, and colloids. A nasogastric tube was inserted, and a small amount of bright red blood, believed to be secondary to the trauma of passage, was obtained. Because of this, however, an emergency upper gastrointestinal endoscopy was performed that revealed no bleeding source from the esophagus, stomach, or duodenum. Rhabditiform larvae of *Strongyloides* were recovered from the duodenal aspirate. Plans were instituted to perform emergency angiography to pinpoint the source of bleeding, but because of the patient's hemodynamic instability and continued bleeding, an exploratory celiotomy was necessary. The small intestine appeared grossly normal. The large bowel was dilated from the ileocecal valve to the sigmoid colon. It was firm and bluish in color and exhibited no haustrations. There was massive mesenteric lymphadenopathy and evidence of fat migration onto the colonic wall. An enterotomy prior to the fashioning of an end ileostomy showed no bleeding from above and a competent ileocecal valve. A subtotal colectomy with exteriorization of the distal part of the sigmoid colon as a mucus fistula was performed.

The specimen consisted of 72 cm of large intestine including cecum with appendix; ascending, transverse, and descending colon, and 8 cm of terminal ileum. The serosa appeared smooth and glistening, with some fat extension toward the nonmesenteric surface. Ten lymph nodes varying in size from 0.3 cm to 1 cm were recovered from the mesentery. There was marked mucosal and submucosal edema with cobblestoning of the cecum and ascending colon for about 30 cm from the ileocecal valve (Fig 1). The intestinal wall measured between 0.4 to 0.5 cm in this area and from 0.2 to 0.25 cm in the distal part of the colon. Two hemorrhagic erosions measuring 0.2 × 0.4 cm were noted 3 cm and 10 cm distal to the ileocecal valve. The remainder of the intestine was grossly unremarkable. Microscopic examination showed numerous undermined and flask-shaped mucosal erosions throughout the entire colon and terminal ileum (Fig 2). The lamina propria and submucosa were densely infiltrated by plasma cells and eosinophils. A similar inflammatory exudate was noted on the serosa. One of the ulcerations had eroded a submucosal vessel that was presumed to be the source of the severe bleeding (Fig 3). A marked increase in epithelial mucous secretory activity was present, and many mucosal glands were dilated and contained inspissated mucus. Numerous small, noncaseating granulomas were noted in the lamina propria, the submucosa, subserosa, and serosa. Granulomas also were

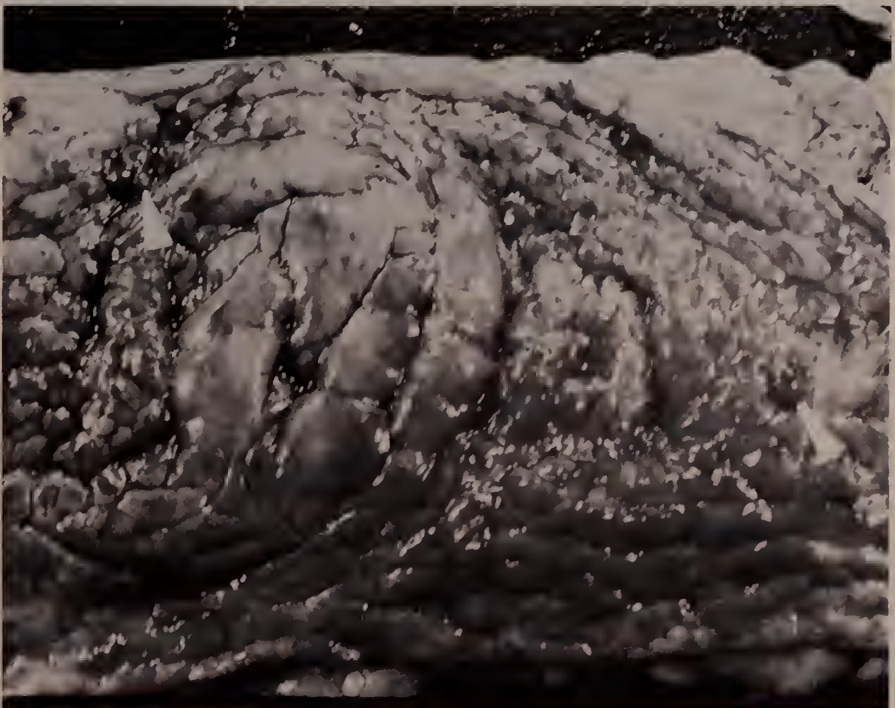

FIGURE 1. Large intestine shows marked cobblestoning due to mucosal and submucosal edema.

From the Departments of Surgery (Drs Dellacona, Spier and Margolis) and Laboratories (Dr Wessely), Queens Hospital Center Affiliation of the Long Island Jewish-Hillside Medical Center, Jamaica, New York.

Address correspondence to Dr Margolis, Director, Department of Surgery, Queens Hospital Center, 82-68 164 St, Jamaica, NY 11432.

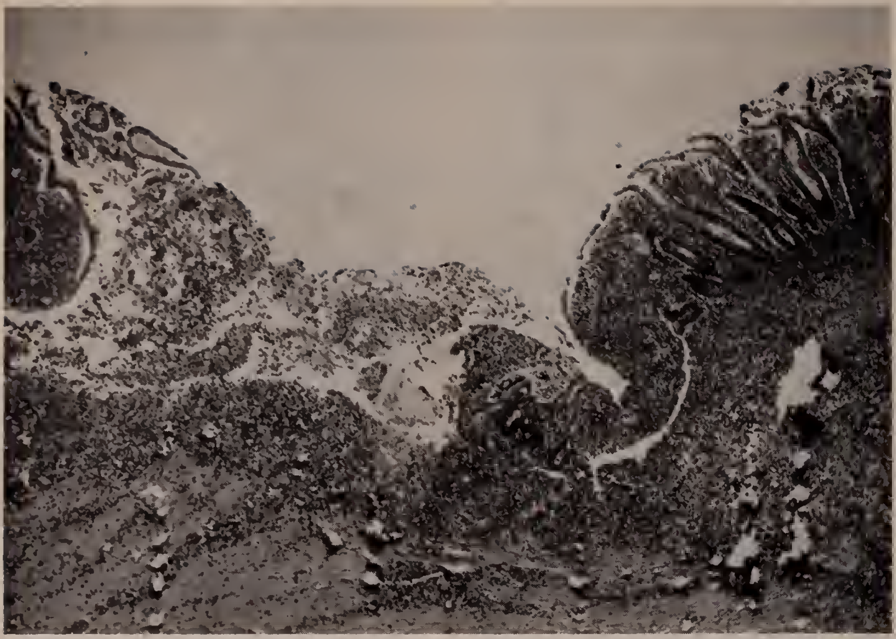

FIGURE 2. Colonic mucosa show flask-shaped erosion (hematoxylin and eosin, original magnification × 300).

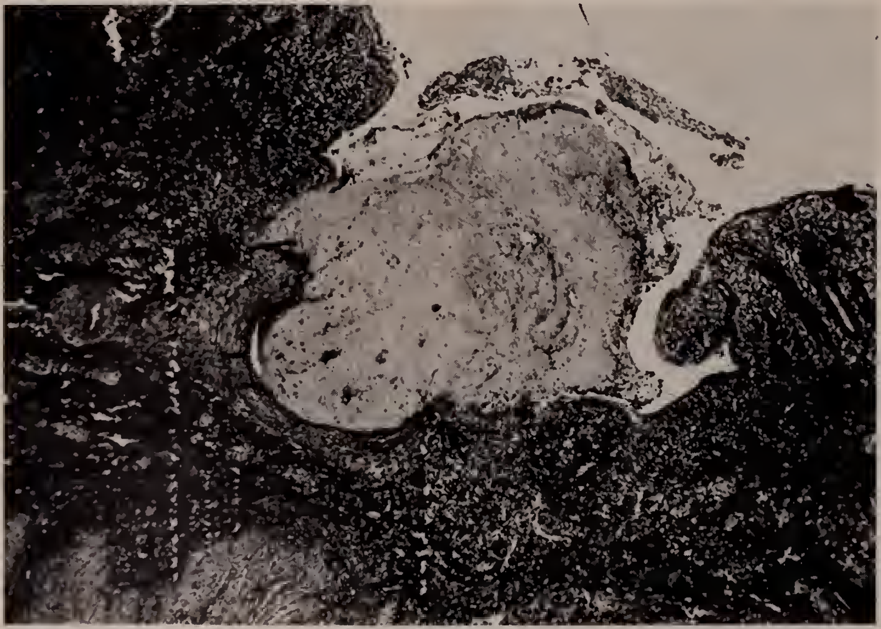

FIGURE 3. Ulceration shows erosion into submucosal vessel (hematoxylin and eosin, original magnification × 300).

seen in the appendix and in some of the lymph nodes. On examining multiple sections, one structure suggestive of a larva was found embedded in mucus, and ova-like structures were seen within a granuloma. Ganglionic swelling and proliferation of the neural elements of the plexus submucosus and, to a lesser degree, of the plexus mesentericus were seen. Submucosal fibrosis was present and marked.

The postoperative course was uncomplicated, and the patient has had no further bleeding. She is currently undergoing an additional six-month course of thiabendazole therapy. After this, her condition is to be evaluated for restoration of intestinal continuity by means of ileosigmoidostomy.

During the postoperative period, we were able to obtain a set of upper and lower gastrointestinal roentgenograms from one of the patient's previous admissions. The duodenum showed disruption of its mucosal pattern, dilation, and diminished motility. There were areas of obliteration of the mucosal pattern with dilation and narrowing in the distal part of the ileum, and deformity of the cecum and ascending colon with a loss of mucosal pattern (Fig 4). Although these changes had been ascribed to Crohn's disease, retrospective analysis at this time shows the findings to be compatible with strongyloidiasis.[1]

Discussion

Strongyloidiasis is a chronic parasitic intestinal infection that has a worldwide distribution. In humans, the disease is produced by the nematode *S stercoralis.* In warm climates, the prevalence of the infection may reach 85%.[2] In the United States, surveys from the southern and border states indicate a prevalence of 0.4% to 4%.[3] The symptoms may be cutaneous, pulmonary, or intestinal. Penetration of the skin by the filariform larvae usually produces only minimal reaction, although the cutaneous manifestations of larva migrans may be seen as in other nematode infestations.[4] A pruritic, papullar, or erythematous rash may be seen with repeated reinfections. After gaining entrance to the body, the larvae pass via the venous system and heart to the lungs, bronchi, and trachea, where they mature into the adolescent form. This phase is frequently asymptomatic; however, a nonproductive cough, wheezing dyspnea, shortness of breath, malaise, headaches, and occasionally a high fever may be seen. The larvae then pass up the trachea and are swallowed. The adult females burrow into the intestinal mucosa, where the eggs are laid. This occurs primarily in the proximal portions of the bowel, although with a heavy parasite burden involvement can be more widespread. Infection may recur from eggs hatching in the intestine and passing through the larval stages (rhabditiform and filariform). The filariform larvae then reenter the host through the ileum or colon, or externally through the skin of the perineal area.[5] The abdominal pain that occurs is often epigastric, colicky, and burning in nature. The pain may be exacerbated by eating. Diarrhea with excess mucus production, alternating with periods of constipation, is common. Distention, nausea, vomiting, weight loss, polymorphonuclear leukocytosis, eosinophilia, anemia, and malabsorption have also been reported.

The diagnosis relies on the identification of rhabditiform larvae in the feces or duodenal drainage. Stool examination should be performed on a fresh specimen, since strongyloides organisms are the only intestinal nematode where larvae rather than eggs are present in the stool.[6] However, if the stool specimen is not fresh, confusion may arise with other nematodes where eggs may hatch into the larval form in the stool. Repeated

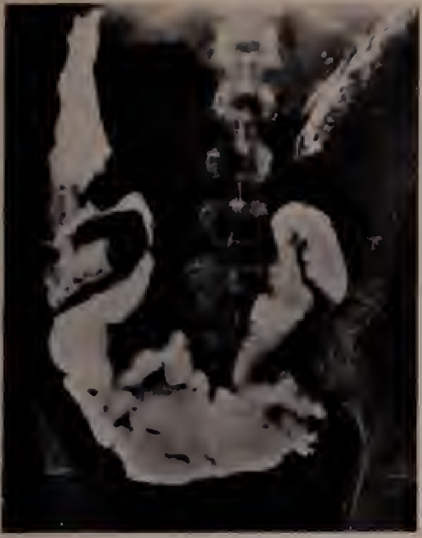

FIGURE 4. X-ray film of upper gastrointestinal series from a previous admission showing deformity of cecum and ascending colon.

stool examinations are required since the discharge of larvae may be intermittent. Duodenal aspiration or duodenal biopsy specimens may yield a diagnosis under these circumstances.

Although the symptoms are seldom severe, it has been demonstrated that *S stercoralis* is an opportunistic agent. In patients suffering from debilitating diseases[7,8] or receiving corticosteroids or other immunosuppressant therapy,[9,10] severe overwhelming infections have been reported. Studies of our patient during the postoperative period showed no evidence of immune system impairment and included plasma electrophoresis and immunophoresis, both of which were within normal limits. There is no apparent explanation for our patient's relative resistance to therapy in the past or for the development of this life-threatening complication on an immunologic basis. Although we suspected the diagnosis of strongyloidiasis as a cause of the hemorrhage before surgery, we chose to perform a total abdominal colectomy in view of the rarity of strongyloidiasis, the previous roentgenographic suspicion of inflammatory bowel disease, and an inability to precisely localize the site of hemorrhage in this patient.

We have been unable to obtain any guidance from the literature as to the advisability of restoring intestinal continuity in this patient by means of an ileoproctostomy. We believe such an approach would permit her to do without her ileostomy and would not add to her risk from further bleeding. More precise localization of the bleeding would be desirable in patients bleeding less aggressively and would permit resection of a smaller segment of the colon.

Acknowledgments. The Department of Radiology of the Queens Hospital Center Affiliation of the Long Island Jewish-Hillside Medical Center cooperated in this study.

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Fatal systemic strongyloidiasis following corticosteroid therapy

FRED KIMMELSTIEL, MD, MICHAEL LANGE, MD

Strongyloides stercoralis is an intestinal nematode that can produce serious infections in man, usually under extreme circumstances. These include debilitating diseases that depress the cell-mediated immune system or disorders that require immunosuppressive or corticosteroid therapy. Previous reports have described patients, particularly in endemic regions such as Africa and South America, with disorders of the immune system who have succumbed to infection with *Strongyloides.* In this report we describe an unusual case of fatal systemic strongyloidiasis in an otherwise healthy young man who was treated at our institution for head trauma.

CASE REPORT

A 36-year-old Hispanic man presented to the emergency room complaining of progressive crampy abdominal pain and anorexia during a three-week period. On the day of admission he suffered two syncopal episodes and experienced hematemesis and melena. The patient had immigrated to the United States from Puerto Rico more than 30 years ago, and he had had no recent travel outside the United States and no chronic illness. Approximately two months before this admission, he had been hospitalized for one month after sustaining a head injury in a motor vehicle accident. At that time he was brought to the emergency room unresponsive except to deep pain. Roentgenograms of the skull revealed a linear left occipital skull fracture, and a computerized tomography (CT) scan disclosed cerebral contusion with midline shift. A CBC obtained on admission revealed a WBC count of 14,500/mm^3 without eosinophils. The patient was treated with endotracheal intubation, hyperventilation, and high-dose steroid therapy in the form of dexamethasone, 6 mg every four hours. He responded well and the endotra-

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From the Departments of Surgery (Dr Kimmelstiel) and Medicine (Dr Lange), St Luke's-Roosevelt Hospital Center, New York, NY.

Address correspondence to Dr Kimmelstiel, Surgical Resident, Department of Surgery, St Luke's-Roosevelt Hospital Center, New York, NY 10025.

cheal tube was removed on the day after admission. The dexamethasone dose was being tapered when, on the sixth hospital day, the patient was noted to be disoriented; there was no other measurable change in the neurologic examination. Repeat CT scan showed an infarct in the right frontoparietal region secondary to contusion. The dexamethasone dose was increased (to 6 mg every four hours) without initial improvement. However, over the next several days his mental status cleared, and dexamethasone therapy was tapered and discontinued after a two-week period, at which time he was discharged with no medication.

On his final admission, the patient was found to be hypotensive with a systolic blood pressure of 50 mm Hg palpable, and a pulse rate of 110/min. Physical examination revealed a mildly distended, diffusely tender abdomen with maximal tenderness in the epigastrium but without peritoneal signs. Rectal examination revealed guaiac-negative stool, and nasogastric aspiration yielded a small amount of coffee-ground material. The hematocrit reading was 26% and the initial impression was an upper gastrointestinal hemorrhage. The patient was given normal saline solution intravenously for resuscitation. Other laboratory values included a WBC count of 32,400/mm^3 with 54 band forms and 2 eosinophils. Albumin was 0.8 g/dL, serum calcium was 4.8 mg/dL, total bilirubin was 2.9 mg/dL, and serum amylase 10 U/dL. The patient's respiratory status progressively deteriorated and he required mechanical ventilation. Because of persistent hypotension, he was treated with intravenous dopamine, norepinephrine, and dobutamine. It was thought that he might have necrotizing pancreatitis. Peritoneal lavage recovered 3 L of straw-colored ascitic fluid that contained 1,102 WBC/mm^3 and the amylase was 101 U/dL. Microscopic examination of the ascitic fluid revealed worms that were identified as the filariform larvae of *Strongyloides stercoralis* (Fig 1). Cultures of blood, urine, and sputum were negative. The patient was given thiabendazole, 1,500 mg, the drug of choice for strongyloidiasis. His condition continued to deteriorate, and he died on his third hospital day, 12 hours after receiving his first dose of thiabendazole. Postmortem examination revealed massive infection with *S stercoralis* including the stomach, entire small bowel, cecum, ascitic fluid (Fig 2), liver, and lungs. Hepatomegaly with parasitic invasion of the sinusoids was described. There were bilateral pulmonary infiltrates secondary to overwhelming strongyloides infection that caused severe respiratory compromise. The lesions in the small bowel and cecum consisted of large, multiple superficial and deep ulcerations that resulted in severe protein-losing enteropathy.

DISCUSSION

Strongyloides stercoralis can complete its life cycle either in human subjects or independently in the soil. In the soil, it retains its infectious potential at the filariform larval stage. The larvae can penetrate skin and reach the venous system and then the lungs by way of the lymphatic system. The larvae penetrate the alveolar spaces of the lung and migrate up the trachea to the glottis and are then swallowed. They eventually reach the upper part of the small bowel, their site of predilection. There the mature female lays up to 40 eggs daily, which transform into the rhabditiform larvae that are passed in the stool. Some of the rhabditiform larvae may metamorphose into the filariform type. These can then invade the gut wall or perianal skin producing a repetitive endogenous cycle termed autoinfection. Through this process a host may retain a worm burden for up to 30 years after leaving an endemic region.[1,2] *Strongyloides stercoralis* is found throughout the world, including parts of Africa, South America, and Puerto Rico. In the United States, eastern Kentucky, Tennessee, southern Louisiana, and parts of Appalachia are considered endemic regions. Most patients with strongyloides infections are asymptomatic. Up to 50% will have mild abdominal complaints, pain, weight loss, and diarrhea. Eosinophilia is common and its presence should raise suspicion of strongyloides infection.

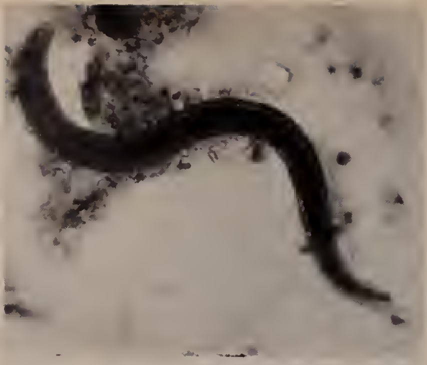

FIGURE 1. Filariform larva of *S stercoralis* recovered from peritoneal lavage effluent and discovered on cell count.

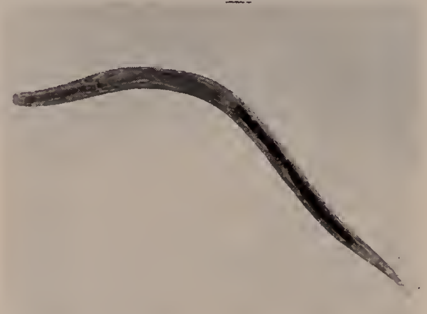

FIGURE 2. Larval form recovered from ascitic fluid at postmortem examination.

Some patients with strongyloides infection present with a systemic form of the disease that is frequently fatal and often diagnosed only at postmortem examination.[1,2] It has been documented that the administration of corticosteroids given over a significant period of time increases the worm burden and the transformation rate to the infectious filariform larvae.[3-5] With few exceptions, this has been seen in patients treated with steroids for several months or longer, in whom an underlying disease has already caused a defect in their cell-mediated immunity. This accelerated form of strongyloides infection has been reported more commonly in patients undergoing organ transplantation, in patients receiving cancer chemotherapy with its resultant immunosuppression, or in patients with chronic protein-calorie malnutrition states.

Our patient showed several classic aspects of the disseminated form of strongyloides infection. Patients such as these, in contrast to those with the asymptomatic or milder form, do not have significant eosinophilia. This is not due solely to the steroid effect upon eosinophils.[1] The albumin level is low partially due to the initial disease process and also to infection of the bowel by the filariform larvae resulting in a protein-losing enteropathy as well as a malabsorption syndrome.[1-3,6] In contrast to our patient, systemic strongyloidiasis is frequently accompanied by an enteric bacteremia as a consequence of the "hyperinfection syndrome." Therefore, immunosuppressed patients who have positive blood cultures with different enteric organisms, but without an obvious source of entry, may need to be investigated by duodenal aspiration for strongyloides infection.[2]

Ascitic fluid has seldom been examined in patients with systemic strongyloidiasis. These patients often have significant ascites, and the filariform larvae can be recovered due to their ability to traverse the bowel wall.[7] Abdominal paracentesis may, therefore, be one way to confirm the diagnosis of strongyloidiasis in these patients. However, this can be accomplished more simply with a direct stool examination that will identify the parasite and that should be performed in all patients in whom this diagnosis is suspected. Stool examination and differential blood counts should also be performed prior to treatment of any patient from a known endemic region.

Recent reports have demonstrated the

ineffectiveness of high-dose steroid therapy in patients with acute head injury and secondary intracranial hypertension. This is in contrast to the well-documented efficacy of steroids in the treatment of intracranial hypertension not associated with trauma. For example, steroids have been shown to be of benefit in the treatment of cerebral edema secondary to intracranial neoplasms.[8-10]

This patient demonstrates the detrimental effects of steroid therapy in a trauma patient who had no underlying chronic debilitating disease and who had left an endemic region more than 30 years prior to the institution of steroid therapy. The case also illustrates the importance of evaluating all patients from endemic regions for parasitoses at the outset of treatment. The rapidly fatal course in this patient, one month after the withdrawal of steroids, due to invasive strongyloidiasis was dramatic and may demand reappraisal of the treatment of a patient with head injury and a more judicious use of steroid therapy in general.

Acknowledgment. The authors thank Dr Edward Stanley-Brown for his kind assistance in the preparation of this manuscript.

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Herniation of the heart

A complication of intrapericardial pneumonectomy

MARK GINSBURG, MD, ANDREW MANGANARO, MD, ROBERT WEINER, MD

Cardiac herniation following intrapericardial pneumonectomy was first recognized by Bettmann and Tannenbaum in 1948.[1] Since then, there have been frequent reports of this complication. When unrecognized, it has been fatal. We present a case in which the diagnosis of herniation was delayed, yet the patient survived. The etiology, presentation, and pathophysiology of this and previous cases in the literature are reviewed. We believe postpneumonectomy herniation of the heart is preventable, and techniques to repair the pericardial defect are descibed.

CASE REPORT

A 53-year-old man was admitted to the hospital on January 7, 1981, after an annual chest film showed a right hilar mass. He had smoked cigarettes for many years, and in the preceding three weeks he had coughed up blood. A bronchoscopy performed on January 8 demonstrated a large fungating tumor protruding from the right upper lobe bronchus 1.5 cm from the carina. Bronchial brushings were suspicious for carcinoma.

On January 13, a right pneumonectomy was performed. Dense inflammation was found around the right pulmonary artery. The pericardium was opened, and control of the main pulmonary artery was achieved within the pericardium. After resection, the pericardium was approximated to the adventitia of the vena cava. The chest was closed without an intrapleural drain in place.

The patient did well initially. The postoperative chest film did not show a mediastinal shift. Approximately five hours after surgery, the patient became mildly hypotensive. At this time, an electrocardiogram showed T-wave inversion in leads I, II, AVR, and AVL; and new q waves in leads V_1 and V_2. The patient was thought to have a myocardial infarction, and an attempt was made to place a Swan-Ganz catheter. This, however, could not be advanced into the right atrium. A chest film (Fig 1) showed that the heart had shifted to the right side. Eleven hours after surgery the patient's blood pressure dropped precipitously. A diagnosis of cardiac herniation was made, and the previous thoracotomy incision was opened in the Intensive Care Unit. The heart was found to have herniated through the pericardial defect into the right hemithorax. It was manually replaced into the pericardial sac with rapid return to a normal pulse and blood pressure. The patient was returned to the operating room where a flap of posterior parietal pleura was advanced over the pericardial defect. The flap was sutured to the edges of the pericardium and was reinforced with numerous Dacron pledgets. The hemithorax was generously lavaged with antibiotic solution, and the chest was closed.

The patient required moderate pharmacologic support (dopamine and nitroprusside) for 24 hours after surgery and 10 days of mechanical ventilation. A superficial wound infection was treated with antibiotics and local care. The EKG returned to normal, and cardiac enzymes were in the normal range.

The patient made a full recovery and was discharged on the 21st postoperative day.

DISCUSSION

The intrapericardial approach to the lung root for pneumonectomy was first described by Allison in 1945.[2] It allowed a more radical resection of carcinoma, while at the same time providing greater control of major pulmonary vessels. In 1948 Bettmann and Tannenbaum[1] reported a catastrophic complication of this procedure, namely, subluxation of the heart through the pericardial defect.

A search of the literature revealed 28 cases of cardiac herniation related to pneumonectomy.[1,4-11] Twenty-three

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From the Department of Surgery, Rochester General Hospital (Drs Ginsburg, Manganaro), and The University of Rochester, School of Medicine and Dentistry (Dr Weiner), Rochester, NY.

Address correspondence to Dr Ginsburg, Resident in Surgery, Strong Memorial Hospital, Department of Surgery, 601 Elmwood Ave, Rochester, NY 14642.

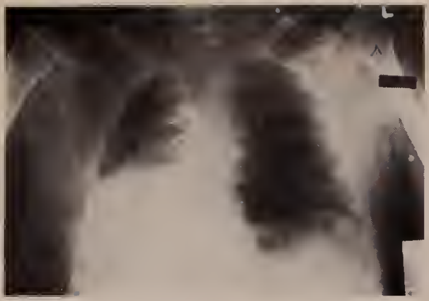

FIGURE 1. Chest film showing right-sided cardiac herniation.

cases occurred in men. Herniation occurred more often on the right side (17 cases) than on the left (11 cases). It usually occurred within the first two hours after operation (70 percent), and always within the first 24 postoperative hours.

Hypotension developed in all patients; several had a cardiac arrest. Many showed signs of superior vena cava obstruction, cyanosis of the upper half of the body, and engorged jugular veins. A chest roentgenogram, when obtained, showed the heart occupying the right side of the chest in cases of right-sided herniation, and an abnormal ventricular contour in cases of left-sided herniation.

The correct diagnosis was made in 13 cases (45 percent). In the remaining cases, hemorrhage or myocardial infarction was most often believed to have occurred. In four cases, the diagnosis was established at autopsy. The over-all mortality rate was 43 percent.

The physiologic derangements depended on which side herniation occurred. In right-sided herniation, a gross degree of cardiac dextrorotation takes place that results in obstruction at the atriocaval junction and the ventricular outflow tracts. In left-sided herniation, the ventricles become incarcerated in the pericardial defect. Ischemia and congestion of the entrapped myocardium ensues, leading to infarction or fibrillation.

Yacoub[4] delineated four factors that may lead to herniation: (1) suction applied to chest drainage tubes or aspiration of the hemithorax; (2) rolling the patient on the operative side; (3) hyperinflation of the remaining lung; and (4) violent bouts of coughing often induced by endotracheal suction.

Primary closure and wide excision of the pericardium are both unreliable in preventing herniation. Deiraniya[8] suggested pericardial slings fashioned from the edges of the defect. Levin[5] advocated fascia lata, but this is inconvenient to harvest. We believe that a pleural flap, as described by Schechter,[12] provides the simplest and most reliable closure. This technique was employed in our patient with success.

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Anomalous origin of the left coronary artery from the right coronary sinus

A cause of sudden death

SUMI M. MITSUDO, MD, ALAN M. HIRSCHMAN, MD, DENNISON YOUNG, MD

Although anomalous origin of the left coronary artery from the right coronary sinus (anterior sinus of Valsalva) has been considered a rare malformation of minor clinical importance, a review of the literature reveals 21 children and young adults in whom this anomaly has been associated with sudden, unexpected death during or immediately after physical exertion.[1-11] This report describes a child with this anomaly in whom sudden death unrelated to physical exertion occurred.

CASE REPORT

A nine-year-old boy was brought to the emergency room after having fainted during a church service. There had been no previous undue physical exertion. The church service was described as "sedate," and the boy had been standing quietly at the time of collapse.

On admission, he had a palpable pulse and adequate blood pressure. His breathing was labored, and he was unresponsive to all stimuli. The electrocardiogram (ECG) revealed sinus bradycardia at a rate of 30 to 40 beats per minute, followed by cessation of pulse and no obtainable BP. There was no improvement with endotracheal intubation, appropriate intravenous medications, and cardiopulmonary resuscitation. Ventricular fibrillation developed that was unresponsive to cardioversion, and ultimately, resuscitation attempts were stopped.

On further questioning of the parents, it was learned that the boy had always been in good health except for an unexplained fainting spell one year previously. This had oc-

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From the Departments of Pathology (Dr Mitsudo) and Pediatrics (Drs Hirschman and Young), Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York.

Address correspondence to Dr Mitsudo, Associate Attending Pathologist, Montefiore Medical Center, 111 E 210 St, Bronx, NY 10467.

curred after he had run to catch a bus. He had not complained of chest pain then or at any other time. No medical attention had been sought.

At necropsy, the only important pathologic findings were in the heart, which at 170 g was somewhat heavier than the normal weight (115 g) for the boy's age and size. There was no substantial gross hypertrophy of the ventricles, but pallor of the anterior part of the left ventricular myocardium was noted. The cardiac valves were normal. The left coronary artery, which was of normal size, arose anomalously from the right coronary sinus (anterior sinus of Valsalva) adjacent to the right coronary ostium (Fig 1). The proximal segment of the left coronary artery angled sharply as it exited the aortic wall with consequent flattening of the lumen (Fig 2, left). One centimeter beyond the origin of the left coronary artery there was a plaque-like eccentric thickening of the intima, causing a 50% to 60% narrowing of the lumen (Fig 2, right). The coronary artery then angled sharply to the left and coursed within the adventitia in the sulcus between the base of the aorta and the pulmonary artery. On reaching the anterior wall of the heart, it bifurcated normally into the anterior descending and circumflex arteries.

On microscopic examination, the intimal plaque of the left coronary artery consisted of a loose myxoid ground substance that contained many spindle cells (Fig 3). The myocardium showed moderate ischemic changes characterized by prominent wavy myocardial fibers but no necrosis. Examination of the sinoatrial and atrioventricular nodes revealed no evidence of hemorrhage, necrosis, or fibrosis. The small intramyocardial arteries showed mild intimal thickening.

The lungs weighed 500 g (normal, 300 to 325 g) and showed capillary congestion, moderate pulmonary edema, and focal intra-alveolar hemorrhage. The remaining visceral organs showed only vascular congestion.

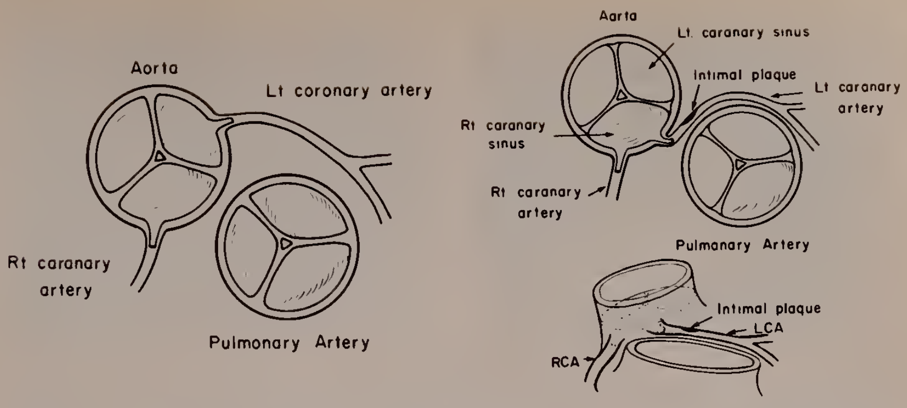

FIGURE 1. Left, normal relationship of coronary arteries to aorta and pulmonary artery; Right, anomalous origin of left coronary artery from right coronary sinus, its course between base of aorta and pulmonary artery, and location of intimal plaque. (Rt, right; Lt, left; RCA, right coronary artery; LCA, left coronary artery)

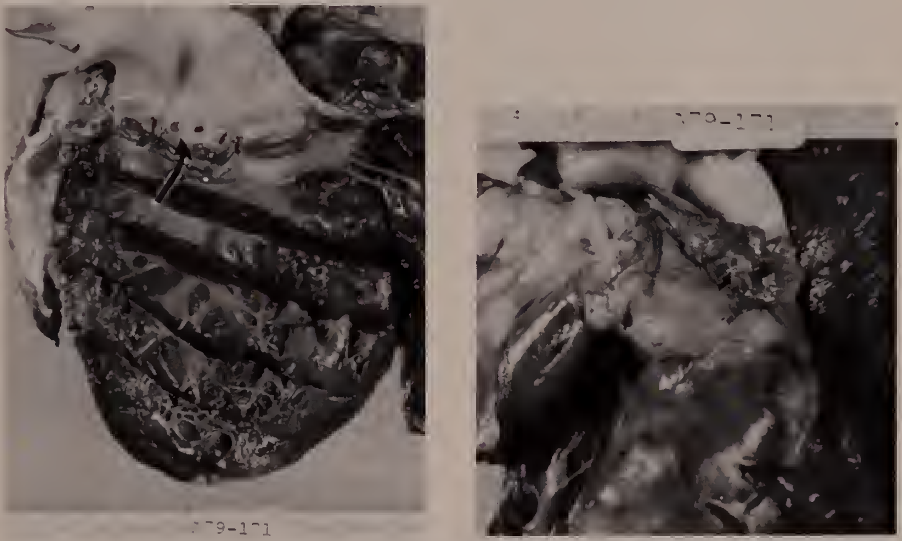

FIGURE 2. Left, heart showing left ventricle and aortic valve—note ostia of coronary arteries in right sinus of Valsalva and sharp angulation at origin of left coronary artery (arrow); Right, epicardial surface of heart showing sectioned surface of left coronary artery containing intimal plaque (arrow).

Discussion

The incidence of anomalies of the coronary arteries in the general population is unknown. In a large autopsy series, Alexander and Griffith[12] reported the frequency of major primary coronary artery malformations to be 0.28%. In a selected population of individuals observed by coronary arteriography, Kimbiris et al[10] found an incidence of malformation of 1%, and Chaitman et al[13] found an 0.83% incidence. The incidence of anomalous origin of the left coronary artery from the right anterior coronary sinus was found by Chaitman et al[13] to be 0.19%, and Moodie et al[14] reported an incidence of 0.02% in similar studies.

Anomalies of the coronary arteries fall into three categories:[15-18]

(1) The major anomalies are usually clinically important and represent an abnormal communication of the high-pressure coronary arterial system with a low-pressure cardiac chamber or vessel. The resulting arteriovenous fistula may lead to cardiac failure, myocardial ischemia, or bacterial endocarditis.

(2) In minor anomalies, the coronary arterial system arises entirely from the aorta or its tributaries, with no abnormal communication with the cardiac chambers, coronary veins, or pulmonary vessels. Such anomalies are represented by an abnormal position of the coronary ostia in the aorta or by stenosis or hypoplasia of a coronary artery, often of minimal, if any importance, but sometimes of major concern.

(3) Coronary artery anomalies may also occur in hearts with major congenital cardiac malformations.

In this case, the coronary artery variations are secondary to congenital malformations such as transposition of the great vessels or tetralogy of Fallot.

The anomalous origin of the left coronary artery from the right anterior coronary sinus found in this patient, while classified as minor (type 2), was of major clinical importance. This anomaly has been described in 58 children and adults in isolated case reviews or composite descriptions of coronary artery anomalies.[1-13] Sudden and unexpected death during or soon after physical exertion has occurred in 21 patients with this anomaly. All were young males from 11 to 21 years old, except for a one-

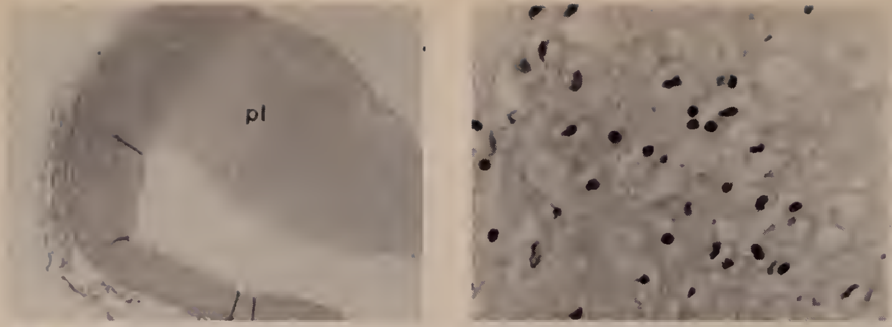

FIGURE 3. Left, histologic appearance of cross-section of left coronary artery containing intimal plaque (PL) (hematoxylin and eosin, original magnification × 25); Right, histologic appearance of plaque, which is composed of spindle cells set in loose myxoid background (hematoxylin and eosin, original magnification × 400).

year-old infant who died during or after a crying spell. The present case is unusual, since the child was standing quietly and had not been engaged in heavy exercise at any time before his collapse.

Sudden death resulting from anomalous aortic origin of the coronary arteries occurs only when the left coronary artery arises as a single or double vessel from the right sinus of Valsalva and then passes sharply leftward and posteriorly between the aorta and the pulmonary artery (Fig 2, left). Not all patients with this anatomic variant die suddenly, however, and apparently additional compromise of the aberrant vessel is required.

Cheitlin et al[7] have suggested that the acute leftward passage of the artery along the aortic wall causes the entrance into the left coronary artery to be slit-like. With increased expansion of the aorta and pulmonary artery during exercise, the left coronary artery is stretched, resulting in a flap-like closure of the orifice with sudden myocardial ischemia. An alternative explanation has been advanced by Liberthson et al.[9] They postulated that with elevation of cardiac output and systemic and pulmonic pressure during periods of exercise, the aorta and pulmonary artery dilate, causing kinking of the coronary artery as it is forced to turn even more sharply between the two great vessels. This in turn results in ischemia from decreased coronary artery flow (Fig 1, right).

Additional anatomic abnormalities of the aberrant left coronary artery have also been described. One 17-year-old boy showed severe atherosclerotic stenosis localized to the segment of presumed chronic compression of the left coronary artery between the aorta and the right ventricular infundibulum. Anomalous congenitally small left coronary arteries, believed to limit coronary artery flow during exercise, have also been demonstrated in some instances of sudden death in athletes.[5,6]

The most likely mechanism for compromise of coronary artery blood flow seems to be that suggested by Cheitlin et al,[7] and appears to fit the anatomic condition in our patient. In addition, coronary artery blood flow was further compromised by the intimal plaque, which narrowed the lumen to less than 50% of its normal size. This plaque may be the result of the jet-like pressure of the blood entering the left coronary artery.

As emphasized by Lown,[18] the problem of sudden cardiac death includes an acute precipitating mechanism, which may be physical or emotional stress, and the presence of chronic electrical instability of the myocardium resulting from regional ischemia and malperfusion. Regional malperfusion provides conditions for nonhomogeneity of cardiac muscle. Contributing to the nonhomogeneity are inadequate local oxygenation, impaired substrate delivery, varying degrees of muscle-fiber stretch, unequal metabolite accumulation, and pressure gradients that vary with the relation of the underperfused area to endocardial or epicardial surfaces. Enhanced nonhomogeneity of muscle in relation to the duration of the refractory period favors the development of ventricular automaticity, reentrant tachycardias, and ventricular fibrillation.[19]

Due to the rapid death in this patient, necrosis had not occurred, but ischemic changes in the myocardium were demonstrated at postmortem examination. Despite the absence of a demonstrable precipitating mechanism, it is reasonable to assume that the myocardial ischemia was responsible for regional malperfusion and the consequent arrhythmic death.

Sudden death from exertion is the usual initial and final event in patients with anomalous aortic origin of the left coronary artery, with the diagnosis first made at autopsy. Based on recognition of premonitory exertional symptoms and appropriate investigation, however, two adolescents have undergone successful coronary artery surgery.[7,20] It is unfortunate, therefore, that further investigation had not been carried out for our patient subsequent to his initial syncopal attack one year previously. At that time, noninvasive studies such as stress testing, thallium myocardial imaging,[21] and two-dimensional echocardiography[22] might have provided sufficient information to justify coronary arteriography for full anatomic definition, followed by an appropriate surgical procedure.

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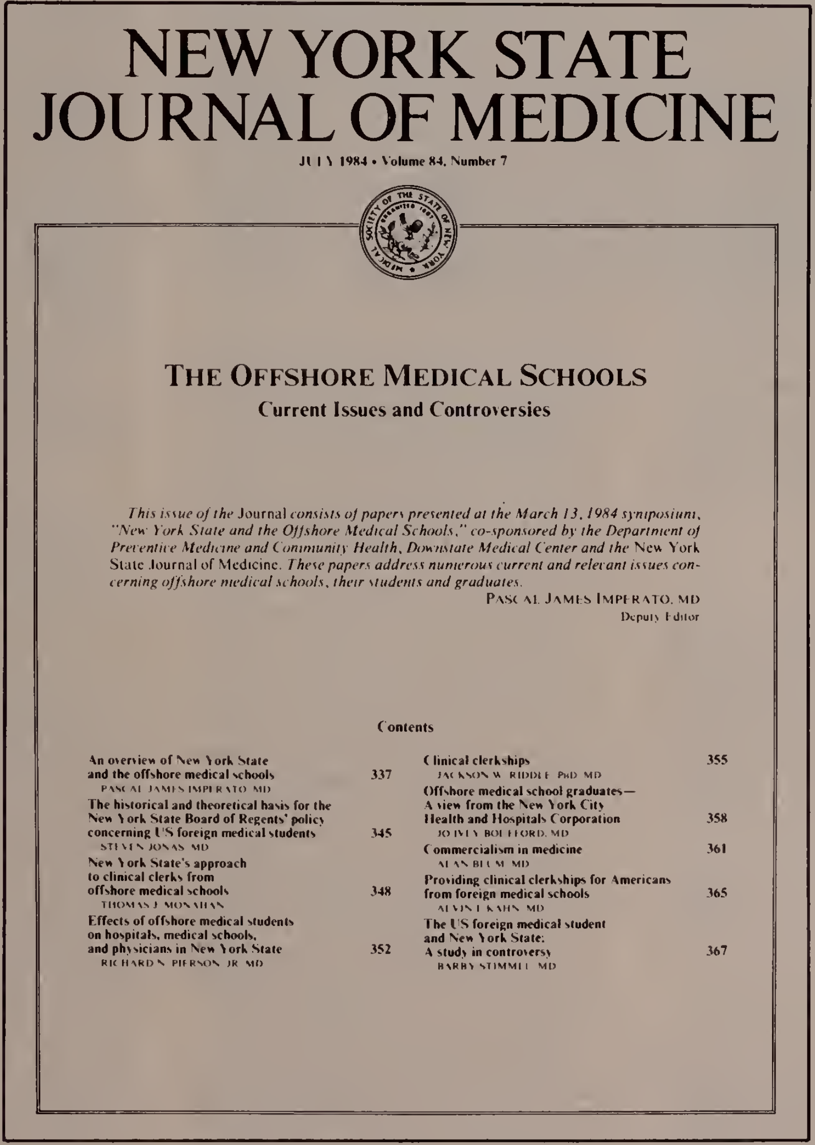
LIMITED OFFER



NEW YORK STATE
JOURNAL OF MEDICINE

JULY 1984 • Volume 84, Number 7

THE OFFSHORE MEDICAL SCHOOLS

Current Issues and Controversies

This issue of the Journal *consists of papers presented at the March 13, 1984 symposium, "New York State and the Offshore Medical Schools," co-sponsored by the Department of Preventive Medicine and Community Health, Downstate Medical Center and the* New York State Journal of Medicine. *These papers address numerous current and relevant issues concerning offshore medical schools, their students and graduates.*

PASCAL JAMES IMPERATO, MD
Deputy Editor

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The July issue of the *Journal* is a timely and authoritative overview of one of the most controversial subjects in health care. A limited number of copies remains. They can be purchased for $4.00 from the New York State Journal of Medicine, 420 Lakeville Road, Lake Success, NY 10042.

NYJ NEWS FEATURES

Will prescription drugs be advertised to the general public?

Companies getting ready 'just in case'

Direct-to-consumer prescription drug advertising is probably a bad, if not unfeasible idea, according to consumer groups, the medical profession, and a surprising number of pharmaceutical companies. Advertising firms question their ability to create ads, particularly television ads, that are clear rather than confusing to the consumer.

Yet even with these dubious appraisals of prescription drug advertising to the consumer (PDAC), "everyone is getting ready, just in case someone else jumps in," according to a source in the Food and Drug Administration (FDA). The FDA has conducted advertising tests for two fictitious drug products, CBS and other potential carriers of advertising have tested markets, and the drug companies themselves have produced model ads and researched cost, liability and consumer and physician receptivity.

At a PDAC symposium in Washington, DC on April 30–May 1, approximately 300 attendees representing consumer groups, federal agencies, industry, the medical profession, advertising concerns, the media, and legal observers concurred that although PDAC may not be in the best interests of the industry or the consumer, it is inevitable.

The symposium was co-sponsored by the University of Illinois at Chicago—and chaired by Alexander M. Schmidt, MD, former FDA commissioner and current vice chancellor for Health Affairs at the university—and SRI International. It was underwritten by the Upjohn Company, Kalamazoo, MI, and coordinated by PW Communications, Inc, New York, publishers of controlled circulation magazines such as *Hospital Physician.*

Since the voluntary moratorium on PDAC was called by then FDA commissioner Arthur Hull Hayes, MD in February 1983, the agency has sought out the views of the interested participants in the issue. Acting commissioner Mark Novitch, MD noted that the agency has not arrived at a final position and is considering various issues: Would direct-to-consumer advertising confuse or mislead patients? Would such advertising compromise the doctor-patient relationship? Would direct-to-consumer advertising trivialize the significance of prescription drugs in the minds of consumers?

The FDA's fictitious prescription drug ads, formatted for both television and magazines, were tested on approximately 1,500 subjects recruited at random in Buffalo, Cleveland, Houston, and Seattle. Louis A. Morris, PhD, of the FDA's division of drug advertising and labeling, summarized the results, reporting that advertisements that contained a large amount of risk information successfully communicated the material without producing "information overload." Many individuals, however, reported mistaken impressions of the drugs, including misinterpretations of their therapeutic purposes. Drug benefits were recalled with greater frequency than risk information.

Morris emphasized that the FDA studies were not designed to conclude whether prescription drugs should or should not be permitted to be advertised to the public, but rather to investigate the applicability of the "brief summary concept" to consumer advertising.

Novitch stated, "The study does suggest that it may be time to explore the next stage of research. To accomplish this goal, we are drafting a proposed regulation that would govern the actual testing in the marketplace under carefully defined conditions." He explained that the objectives of the regulation will be to provide a mechanism that would permit a waiver of the current regulatory requirements and to provide for agency clearance of testing protocols in order to assure that the consumer advertising to be tested is likely to produce bona fide research data. "Such FDA waivers, however, should not be considered as a declaration of 'open season'," Novitch stipulated. "All protocols would be carefully scrutinized to assure that the proposed 'research' is just that," he said.

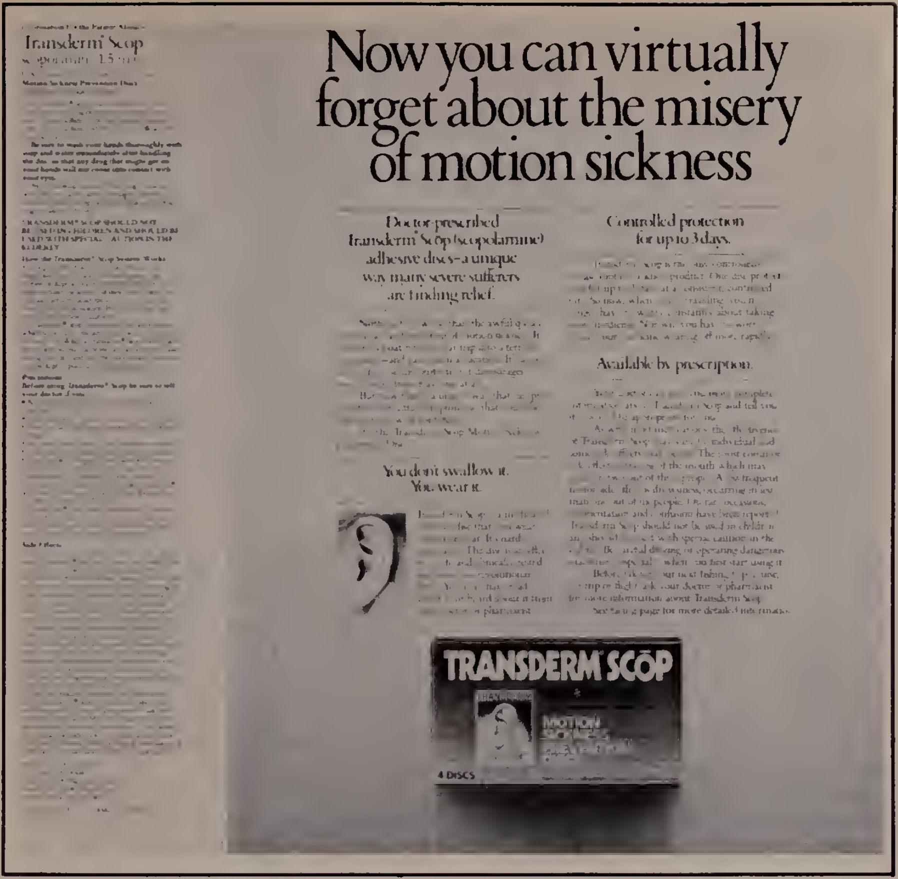
The new regulation would be published in the *Federal Register* and would be open for public comment before any market testing is begun.

INDUSTRY VIEW

Lawrence C. Hoff, executive vice president of the Upjohn Company, said, "My position is that advertising of specific prescription products directly to patients, while looking good to some, has too much potential to harm our medical system for me to support it." He cited five problem areas: cost implications, liability concerns, the potential for patient confusion, effects on the patient-physician relationship, and ethics.

He reported that analysis by Upjohn showed, for example, that the cost to develop ads and purchase air time for the company's top five products—those with the greatest market potential—"could be well in excess of what we are spending today for the promotion of all of our products, for both sales representatives' time and for all non-sales promotion programs." He noted that the cost of advertising, particularly if a competitor advertises and another company is forced to follow suit, will most certainly be passed on to the consumer.

"In a way this issue is an extension of my concern for cost," Hoff noted, ex-


Transderm Scōp

Now you can virtually forget about the misery of motion sickness

Doctor-prescribed Transderm Scōp (scopolamine) adhesive discs—a unique way many severe sufferers are finding relief.

You don't swallow it. You wear it.

Controlled protection for up to 3 days.

Available by prescription.

TRANSDERM SCŌP
4 DISCS

Advertisements for scopolamine, chlorthiazide, pneumococcal vaccine and other prescription products have either appeared in the mass media or are waiting in the wings.

pressing concerns about liability. He suggested that when manufacturers begin to advertise specific products directly to consumers, especially on television where the impact can be significant, there may be an implied warranty which is magnified by advertising. "In my view, the subject of this conference is not patient information," Hoff stressed. "We are talking specifically about using advertising to promote specific drug products to patients . . . we must consider how this might affect the relationship between doctors and patients."

E. Walter Lange, group vice president for marketing of Eli Lilly & Company, echoed Hoff's analysis, concluding that "PDAC would do little to promote the quality of health care."

Ciba-Geigy's Gary S. Freedman, however, encouraged the testing of PDAC in "the real world" rather than debating the issue in the abstract. As senior vice president for government and public affairs and division counsel, Freedman said that he was not representing Ciba-Geigy as an advocate of direct-to-consumer prescription drugs. "We are not certain that such promotion will even serve our commercial interests, and we totally concur with the view that its ultimate justification must include a benefit to the public," he added.

Freedman did provide an example of a proposed program to promote Transderm-Scop, a transdermal patch that contains scopolamine for the prevention of motion sickness, saying that Ciba-Geigy believed that this type of advertisement meets current FDA regulations.

Consumer View

Consumer representatives for the American Association of Retired Persons, the Center for Medical Consumers, the Consumer Federation of America and the National Women's Health Network came down soundly against PDAC.

Arthur A. Levin, MPH, director of the Center for Medical Consumers in New York noted, "The very people (manufacturers favoring advertising) who tell us how anxious they are to educate the public bitterly opposed patient package inserts, and helped end the program before it ever had a chance to get going. I must ask, how believable is their new educational commitment?"

Some observers have noted that both consumer groups and manufacturers have returned to discussions of the patient package insert (PPI) in debating PDAC, and suggest that PPIs may be used as a bargaining point for compromise.

Medical View

The American Medical Association (AMA) does not have a policy on the issue of PDAC, according to Alan R. Nelson, MD, a member of the AMA Board of Trustees. In taking a neutral position, Nelson noted that the AMA is "on record as opposing advertising of prescription drugs that does not give sufficient readily understandable information about potent drugs and their potential adverse effects," adding that the AMA has "supported the dissemination of reliable, understandable and accurate information to the public on matters relating to good health and to illness."

Representatives of the American Academy of Pediatrics (AAP) and the American Academy of Family Physicians vigorously opposed PDAC. Ralph E. Kauffman, MD, a member of the AAP committee on drugs said that exposure of young children and adolescents to intense advertising of potent drugs may encourage drug-oriented attitudes and behavior, and suggested that PDAC may create an inappropriate demand on the physician for medications that may not be in the best interest of the patient.

Richard Penna, PharmD, vice president for professional affairs of the American Pharmaceutical Association (APhA), said, "Pharmacists realize that with PDAC, they will receive more questions from consumers. They like answering questions," he explained, "but they don't like the fact that they [the questions] are stimulated by confusion." The APhA is enjoined from presenting a position on the issue because of a 1981 consent decree with the Justice Department preventing the association from involving itself in certain practices related to advertising of prescription drug products.

Legal View

Much of the regulatory issue, assuming acceptance of PDAC, centered on debate over authority between the FDA and the Federal Trade Commission (FTC). The FDA claims exclusive responsibility, while the FTC position is that the two agencies would have concurrent jurisdiction over PDAC. Working through the regulatory logistics of

PDAC would likely require specific legislation.

James B. Swire, a partner in the New York law firm of Townley & Updike said, "There may be many uncertainties with PDAC, but it is certain to increase product liability." He added that PDAC would undercut the defense of "learned intermediary"—pharmaceutical manufacturers now have a duty to warn only the physician, not the patient, of the dangers inherent in the use of a drug.

William W. Vodra, a partner in the Washington law firm of Arnold & Porter and former associate chief counsel for drugs at the FDA, warned manufacturers that not only would they face regulation by the FDA and the FTC but also by the networks and the advertising media through special requirement standards, by competitors through unfair competition challenges in the courts, and by plaintiff claims of injury or harm from the product.

MEDIA VIEW

Bruce Addison, president and chief executive officer of PW Communications, Inc, in New York, summarized that "media observers have all but locked up PDAC as inevitable." However, Thomas F. Garbett, senior vice president of Doyle, Dane, Bernbach, Inc, in New York and an independent corporate advertising consultant, said that while it is feasible to broadcast advertising messages for almost any type of product or service, the practicality of sustained television advertising for prescription drugs is doubtful.

Garbett added that the high cost of broadcast advertising (particularly television), the inability of many products to support such advertising, and the high incidence of miscomprehension of television messages make the success of PDAC questionable.

The general sentiments of media representatives supported those of John R. Blaney, senior vice president and general manager of Ogilvy & Mather in New York (whose clients include AT&T, Peugeot, and American Express) when he assured pharmaceutical manufacturers, "We're ready when you are."

In concluding the symposium, the chairmen of each group—industry, consumer, medical, legal and media—suggested that more research is required on the effects of advertising on consumer behavior, on benefit/risk information on PDAC and the way in which it is communicated, and on the types of media used and their impact.

Peter Barton Hutt, a partner in the Washington law firm of Covington & Burling and former chief counsel for the FDA, countered, "Research is utterly ridiculous. If you want to find out what happens, go out and do it. We can research any good idea to death." He added, "Seeing whether it will fly in the marketplace is the best test."

C. Joseph Stetler, a partner in the Washington law firm of Dickstein, Shapiro & Morin and former president of the Pharmaceutical Manufacturers Association, called the current FDA moratorium a "cop-out." "Industry must be skeptical of this [PDAC], but there must be an end to the moratorium," he said.

In assessing the PDAC symposium, Milton A. Bass, a member of the Washington law firm of Bass, Ullman & Lustigman and general counsel of the National Association of Pharmaceutical Manufacturers, said, "We have a lack of focus. . . . No one has said they want it [PDAC], or why." Bass said that industry should not support PDAC. "You can expect abuse from the first maverick, and it will require a response from competitors."

"The FDA says they want to do a test to find answers for PDAC. Why do a test?" Bass questioned. The statements and tone of the symposium suggested that no group was strongly in favor of PDAC, he noted. "I'm suggesting that there is no need for a test. There is no need to further pursue this question." He added as an afterthought, "I do wish someone would have presented discussion on the other side of the question."

Carla Carlson

Ms Carlson is a science writer and editor in Washington, DC.

MSSNY POSITION ON DIRECT ADVERTISING OF PRESCRIPTION DRUGS TO LAY PERSONS

Resolution 82-6, "*Direct Advertising of Prescription Drugs to Lay Persons*," called upon the Medical Society of the State of New York to investigate the scope and extent of direct advertising of prescription drugs to lay persons and communicate such information to its membership; that the Medical Society of the State of New York officially take an opposed position to such direct advertisement and communicate it to all members of the Medical Society of the State of New York; that such information and such official position be communicated to all major prescription drug manufacturers; and that this resolution as adopted by the House of Delegates at this annual meeting of the Medical Society of the State of New York be submitted to the American Medical Association by the New York Delegation for consideration by the AMA House of Delegates . . . .

The House referred the original resolution and the amended resolution to the Council for further study. At its meeting on December 16, 1982, the Council referred amended Resolution 82-6 to the Division of Scientific Activities for thorough research, in consultation with General Counsel, and report back to the Council as to recommended disposition of the resolution.

In March of 1983, George J. Lawrence, Jr, MD, Director of the Division of Scientific Activities, and Donald Moy, JD, General Counsel, informed the Council that after studying the original and amended resolutions and the summary of the House discussion, it became evident that the pharmaceutical manufacturers are not advertising illegally when they advertise prescription drugs directly to the public. It was also noted that it is legal for physicians to advertise.

Dr Lawrence and Mr Moy stated that in their opinion the practice of advertising in general cannot be condemned and recommended that MSSNY notify its members, that, if any particular advertisement (by a pharmaceutical manufacturer, or by a physician) is believed to be false, deceptive, or misleading, MSSNY will then pursue this through appropriate channels.

The Council voted to not adopt Resolution 82-6, in accordance with the recommendation of Dr Lawrence and Mr Moy, as it would be inadvisable for MSSNY to oppose advertising, which is legal, unless it is found to be false, deceptive, or misleading.

MOULD ALLERGY

Edited by Yousef Al-Doory, PhD, and Joanne F. Domson, MD. 287 pp, illustrated. Philadelphia, PA, Lea & Febiger, 1984. $28.50 (hardcover).

Most allergists and generalists who deal with allergic problems will be quick to point out that allergies to mould or fungi are the most difficult to diagnose and treat. At any allergy meeting one is likely to find a section devoted to the topic, but may still come out with more questions than answers. It was with great enthusiasm, then, that I approached this book. I hoped to learn more to help in my practice but I was somewhat disappointed.

This compilation of chapters on various topics related to moulds attempts to cover more than those subjects related to allergy. The chapters on classification, sampling, and conidia, while standard for a text on fungal disease are, for the most part, superfluous. Those that deal with the well-understood disease entities of bronchopulmonary aspergillosis, aspergilloma and hypersensitivity pneumonitis are up-to-date and well written by qualified individuals in the field.

Those chapters that cover immediate hypersensitivity reactions and the diagnosis and treatment of allergies give many interesting tips on approaching these problems in clinical practice. While mould allergies are accepted as a major problem among the 40 million Americans who have allergies, the treatment for them remains pharmacologic, with the use of bronchodilators and antihistamines as the mainstay. Immunotherapy or allergy injections offer little help in the treatment of mould allergies. Moulds may grow in different ways under the same conditions, and extracts for treatment are difficult to prepare, as one of the authors points out, and, therefore, may be of little therapeutic value.

I did find the book extremely helpful with regard to where one may find moulds in the patient's environment and on climate conditions that may contribute to their growth. Going into one's basement or into a musty barn or a change of weather may affect the mould-sensitive person. Certain foods that incorporate moulds in their production may also have adverse effects on such people.

The book is well organized with excellent illustrations and charts. Some of the chapters are repetitious, but the information taken in context allows for easy flow of the subject matter. There are no major contradictions within the text itself.

Since there are no major texts in the field of allergy that cover the topic, the book in and of itself is unique and serves as a good source for the practitioner. One would have hoped for a section or two by Dr Salvaggio of Tulane University, who is one of the major clinical investigators in this challenging field.

PAUL M. EHRLICH, MD
New York University
Medical Center
New York City 10016

AIRBORNE AND ALLERGENIC POLLEN OF NORTH AMERICA

By Walter H. Lewis, Prathibha Vinay, and Vincent E. Zenger. 254 pp, illustrated. Baltimore, Maryland, The Johns Hopkins Press, 1983. $60.00 (hardcover)

The physician who treats patients with allergies should have a working knowledge of pollens and plants. Familiarity with the geographic distribution and pollinating seasons of important species is a requisite for proper interpretation of the medical history. An appreciation of taxonomic relationships among the various families and genera contributes to an understanding of cross reactivity, since closely related forms usually share common antigens. Some physicians conduct routine pollen sampling surveys, and most allergists find it necessary on occasion to identify a plant specimen.

Some of the botanical data needed for these purposes can be found in standard allergy textbooks, but space limitations generally preclude extensive coverage of the material. There are atlases and collections of photomicrographs that serve as guides to pollen identification and contain some descriptive but sparsely illustrated references dealing with allergenic plants.

The writers of this volume perceived a need for a more comprehensive treatment of the subject. The senior author, a professor of biology at Washington University in St Louis and senior botanist at the Missouri Botanical Garden, and his colleagues, a research associate in biology and an allergy trainee, respectively, at Washington University, have compiled a richly illustrated volume that constitutes an important fund of information about the medically relevant flora of the North American continent.

The scope of the book is largely confined to the plants themselves, their botanical classification, geographic distribution, flowering time, physical appearance and pollen morphology. In addition, there is a brief discussion of the allergenicity of each family or genus, based upon a review of the medical literature and personal communications from a panel of allergists. There is no analysis of the ecologic determinants of pollen distribution or of air sampling techniques, subjects well covered elsewhere, in William Solomon's excellent chapter in Middleton, Reed and Ellis' textbook, *Allergy, Principles and Practice*.

The book begins with a number of color plates of plants photographed in their flowering stages, followed by a series of 136 color photomicrographs of stained pollen. The central section is divided into three chapters devoted to trees and shrubs, grasses and grasslike plants, and weeds and herbs. Within each chapter the different families are presented with their important genera. The text is in many instances supplemented by maps and illustrative tables.

An important element is the book's basic visual orientation. There are numerous black and white photographs, generally of excellent quality, that depict representative species and samples of pollen from each botanical family. Both light microscopy and three-dimensional scanning electron microscopy are used to prepare the pollen photographs so that structural details revealed by the two methods can be compared. The appendix presents 58 pages of maps showing the distribution of important plant species as well as a glossary of technical terms.

Clearly the authors have amassed a large amount of information in compact form, and the book will probably become a frequent reference source. Some aspects of its format, however, might create difficulties for the reader, especially on first exposure. Some of these are unavoidable. The photographs are often separated by several pages from the relevant text, and the complicated captions under the photomicrographs are often unclear. Common names are mentioned in the text headings, but the basic organization of the book is alphabetic by scientific name, so that one finds white oak in the genus *quercus* listed under the title Fagacea, the Beech Family. Fortunately, there is an excellent index.

Some of the reports of allergenicity, especially those involving less important plants, require further documentation, and the book may well serve as a stimulus to future research in this area. The descriptions of pollen morphology use a number of highly technical terms which are defined only in the glossary at the back. The introduction contains a single figure diagramming the pollen wall, and the average reader would benefit from some additional line drawings to illustrate the structural features of pollen grains. There are a number of other places where the clarity of descriptive passages would be enhanced by a supplementary sketch. I noted only one lapse—two photographs of the grasses were inadvertently omitted.

These are only minor flaws. The book itself is a major achievement. It belongs on the allergist's bookshelf and will be an essential addition to the library of any hospital that conducts aeroallergen surveys.

WILLIAM M. NICHOLAS, MD
Long Island Jewish-
Hillside Medical Center
New Hyde Park, NY 11042

PHOTOIMMUNOLOGY

Edited by John A Parrish, MD, Margaret L Kripke, PhD, and Warwick L Morison, MD. 304 pp, illustrated. New York, Plenum Medical Book Company, 1983. $39.50.

Photoimmunology is a composite discipline that combines aspects of dermatology, photobiology, immunobiology and cellular immunology in the study of effects of ultraviolet (UV) irradiation on immune function and the immune system. Although UV effects on the skin, and retrospectively on immune function, were first reported in the late 1930s, it was not until the mid-1970s that the phenomenology was rediscovered within the context of modern cellular immunology. Since then, our understanding of photoimmunologic effects has increased substantially, due primarily to a more complete understanding of the complex mechanisms required for stimulation and control of immune responses.

This volume consists of well-written overviews of relevant aspects of photobiology, immunology and clinical dermatology as they apply to the overall discipline of photoimmunology. The authors of the various chapters comprise a nationally and internationally recognized group of expert clinicians, immunologists and photobiologists. The book is divided into three sections, Principles of Photoimmunology, Experimental Photoimmunology and Clinical Photoimmunology. This organization is appropriate, as it groups the subject matter and provides a continuum for the reader.

Section I deals with the basic physics of UV and visible radiation, the structure and optical properties of skin, and its response to UV light. This is a well written section, providing a clear explanation and discussion of the complex concepts of UV radiation and photosensitization reactions. Judicious use of simple figures and diagrams enhance the text. Chapters 2, 3 and 4 are of particular interest, covering essentials of photosensitization reactions in mammalian cells, experimental photobiology techniques, and optical properties of normal skin—all extremely important in designing meaningful experiments in photoimmunology.

Section II provides a comprehensive review of animal and human studies in photoimmunology. Included in this section are basic mechanisms of immune responses, carcinogenesis and cell biology. The first chapter deals entirely with UV-induced skin cancer and provides a timely discussion and comparison of the properties of UV-induced versus viral- and chemical-induced tumors with respect to immune responsiveness. The second chapter is considerably broader in that it discusses the effects of UV radiation on various immune responses. Although primarily concerned with a detailed analysis of UV effects on delayed-type hypersensitivity reactions that occur in the skin, this chapter also addresses systemic effects of UV radiation on immune responses in general. The final chapter is devoted to the effects of UV radiation on immune reactions in humans. Although limited, it provides an up-to-date overview of the available experimental findings.

The final section of the book concerns the possible involvement of photoimmunologic reactions in various diseases of the skin and blood. Topics covered include solar urticaria, photoallergy, autoimmunity and phototherapy. This section is perhaps the weakest area of the book. Although the authors seem well aware of their respective fields as evidenced by the extensive bibliographies supplied, the material is presented too simply and there is little indication in any of the chapters of what the various findings mean with respect to disease. Unfortunately, much of the interpretation and correlation of the findings with disease is left totally to the reader.

In summary, this book provides useful information on the current status of photoimmunologic research as well as the basic principles of photobiology and photosensitization reactions. Extensive bibliographies are provided. Students and established investigators alike should benefit greatly from reading this book.

JOHN MOOREHEAD, PhD
University of Colorado
Health Sciences Center
Denver, CO 80220

VITILIGO AND OTHER HYPOMELANOSES OF HAIR AND SKIN

By Jean-Paul Ortonne, MD, David B Mosher, MD, and Thomas B Fitzpatrick, MD. 683 pp, illustrated. New York and London, Plenum Medical Book Company, 1983. $79.50.

Professor Fitzpatrick has focused his career and those of his colleagues and trainees on bringing first rank scientific thought and investigational techniques to a relatively arrid academic dermatologic scene. With the exceptions of New York University and University of California immunology groups, and infectious disease and biochemically oriented academic dermatologists elsewhere, contemporary American academic dermatologic progress has originated either from Fitzpatrick and his trainees or from outside of dermatology. Fitzpatrick's seminal *Dermatology in General Medicine*, now in its third edition, gave to dermatology and medicine a textbook comparable in scope and depth to those of Cecil and Loeb and of Harrison in *Internal Medicine.*

If his lasting renown comes from training the emerging leaders of academic dermatology and his chief editorship of a modern classic text, his personal triumphs have been in the areas of the photobiology and the pigmentary disorders of skin. Thus, the publishing of a major new work, *Vitiligo and Other Hypomelanoses of Hair and Skin* promises to be a significant contribution. Fitzpatrick and his colleague David Moser from Massachusetts General Hospital were joined by Jean-Paul Ortonne of the Hôpital Pasteur in Nice in this new text on the depigmenting disorders, the first in many decades.

The new work is organized along traditional lines of the morphology, distribution, and genetics of the myriad hypopigmenting skin disorders. The spectrum of hypomelanosis, from albinism to the presence of Ziprkowski-Margolis syndrome (a familial hypo- and hyperpigmenting disorder associated with deaf-mutism, a heterochromic iris, and depigmented hair) in a single Egyptian family, encompasses more than a hundred disorders. These include many as rare as Ziprkowski-Margolis syndrome and several as common as the hypomelanosis of the superficial fungal affliction, tinea versicolor, seen on every sunny beach. It is in its mere coverage of this multitude that this book will have its greatest success. It is in the clinic and on the wards that the organization of the book, with its emphasis on differential diagnosis, will come into its own.

The largest section encompasses the congenital and genetic disorders, of which vitiligo is most important and extremely well covered. The vitiligo chapter could easily stand alone as a monograph, and the nearly 200 pages afforded this magnificent review make it both the centerpiece and standard of comparison for the rest of the book. Much of the rest is rather sketchily covered, perhaps because of the relative paucity of contemporary advances. Chediak-Higashi syndrome, an autosomal recessive oculocutaneous syndrome with lipid, reticuloendothelial, hematologic and neurologic findings, and with nearly ideal animal models, is a positive exception, as are the exogenous chemical hypomelanoses and genetic aminoacidoses.

In many ways *Vitiligo and Other Hypomelanoses of Hair and Skin* is a throw back to the classic dermatologic textbook of morphologic and anatomical classification, whose demise was heralded by Fitzpatrick's *Dermatology in General Medicine.* As such it does not entirely fulfill the promise of its origins. On the other hand, a subject not well classified cannot be well studied. The authors have provided a classification and overview of this important diagnostic group that will have to be in every dermatology collection, clinic, and consulting room. It is also destined to markedly improve the quality of written consultations on pigmentary disorders in hospitals across the land.

THOMAS E. DRAKE, MD
Children's Hospital of San Francisco
San Francisco, CA 94108

THE PHYSIOLOGY OF HEMOSTASIS

By Derek Ogston, PhD. 378 pp, illustrated. Cambridge, MA, Harvard University Press, 1983. $27.50.

The field of hemostasis has become populated with basic scientists and clinical researchers. This is reflected in hematology textbooks, as well as in recent volumes devoted to hemostasis and thromboembolic disease. In such texts, introductory chapters describe the biochemistry and physiology of hemostatic elements, and the remaining chapters discuss abnormalities of the four major subdivisions of hemostasis (vascular endothelium, platelets, clotting factors, inhibitors and control mechanisms). Ogston likewise takes this approach with the exception that disease states and therapy are excluded and biological and physiological influences upon normal hemostasis are examined. Ogston is eminently qualified to write such a volume, particularly in the areas of the fibrinolytic mechanism, complement and kinin/kallikrein interactions, and environmental influences on hemostasis, subjects in which he has made significant contributions.

The information in the volume is current, containing discussions of calmodulin, thrombospondin, Protein C, Protein S, histidine-rich glycoprotein, and recent advances in platelet surface glycoprotein structure. References are complete and represent a major source work for research in hemostasis. Nearly one third of the book is devoted to the fibrinolytic and complement systems, subjects of particular interest to Ogston, and these chapters are valuable sources of information. The second part of this book, the physiologic influences on normal hemostasis, contains sections difficult to find in any textbook. These sections are relevant to clinical investigators who must be aware of the variations in normal hemostasis when investigating "abnormal" states.

Ogston achieves his purpose of presenting hemostasis and its physiologic variability in a readable manner. Clearly, however, this book is too complete for a medical student or undergraduate and not complete enough for a clinician. The basic scientist and clinical investigator will find worthwhile information. With the exception of several typographical errors, particularly in the first two thirds of the book, a slightly misplaced Fig 3.16 (should be several pages back under F XIII), and repeated definitions of "kringle," the book is pleasingly presented, with clear tables, figures, and type.

Areas that are insufficiently covered include a chapter devoted to endothelial cell physiology, a subject at least as important as alterations induced by altitude and temperature changes. The role of the endothelium in lipid metabolism and the "natural" process of atherogenesis (admittedly pathological, but universal and of relevance in aging) is not covered. Rheologic properties of blood, which have particular relevance to hemostasis and thrombosis are likewise not discussed. Although one page is devoted to platelet function studies, including methods that are rarely used, a section devoted to biological, chromogenic, and immunoassays might be very helpful.

With the exception of some of the chapters describing physiologic variation, almost all the other information may be found in current hematology texts or those devoted to hemostasis and thrombosis (e.g. *Haemostasis and Thrombosis* edited by Thomas and Bloom of which Ogston is a contributing author, is, in fact, more complete in most areas). The latter volumes are likely to be found in the hematologist's office and in the *Journal of Biological Chemistry* in the basic scientist's laboratory, and therefore, the need to purchase this book (reasonable at $27.50, considering other texts), is questionable.

SANFORD J KEMPIN, MD
Memorial Sloan Kettering Cancer Center
New York City 10021

BOOKS RECEIVED

ANATOMY

Review of Gross Anatomy. Fifth Edition. By Ben Pansky, PhD, MD. 585 pp, illustrated. New York, Macmillan Publishing Co, 1984. $24.95 (softcover)

ANESTHESIOLOGY

Clinical Anesthesia in Neurosurgery. By Elizabeth A. M. Frost, MB, ChB. 480 pp, illustrated. Massachusetts, Butterworth Publishers, 1984. $49.95 (hardcover)

CARDIOLOGY

Guide to Interpreting 12-Lead ECG's. By J. Marcus Wharton, MD, Nora Goldschlager, MD. 248 pp, illustrated. New Jersey, Medical Economics Books, 1984. $19.95 (paperback)

How to Read an ECG. Third Edition. By Margaret G. Blowers, RN, Roberta Smith Sims, RN. 66 pp, illustrated. New Jersey, Medical Economics Company, 1984. $11.95 (paperback)

DERMATOLOGY

The Lives of Lesions. Chronology in Dermatopathology. By A. Bernard Ackerman, MD and Anna Ragaz, MD. 252 pp, illustrated. New York, Masson Publishing USA, Inc, 1984. $75.00 (hardcover)

EMERGENCY MEDICINE

The Practice of Emergency Care. Second Edition. By James H. Cosgriff, Jr, MD and Diann Laden Anderson, RN, MN. 652 pp, illustrated. Pennsylvania, JB Lippincott Company, 1984. $34.50 (hardcover)

ENDOCRINOLOGY

Psychoneuroendocrine Dysfunction. Edited by Nandkumar S. Shah, PhD, Alexander G. Donald, MD. 636 pp, illustrated. New York, Plenum Medical Book Company, 1984. $79.50 (hardcover)

GERONTOLOGY

Clinical Aspects of Aging. Second Edition. By William Reichel, MD. 642 pp, illustrated. Maryland, Williams & Wilkins, 1983. $49.95 (hardcover)

Color Atlas of Geriatric Medicine. By Asif Kamal, MD, J.C. Brocklehurst, MD. 176 pages, illustrated. New Jersey, Medical Economics Books, 1984. $59.95 (hardcover)

HEALTH CARE

Reforming Medicine. Lessons of the Last Quarter Century. Edited by Victor W. Sidel and Ruth Sidel. 311 pp. New York, Pantheon Books, 1984. $9.95 (paperback)

HEMATOLOGY

Hematology: Principles and Procedures. Fourth Edition. By Barbara A. Brown, BA, MT (ASCP), MS. 405 pp, illustrated. Pennsylvania, Lea & Febiger, 1984. $26.50 (hardcover)

HISTORY OF MEDICINE

African Fever. By Dennis G. Carlson. 108 pp. Massachusetts, Watson Publishing International, 1984. $15.95 (cloth)

The Clinical Consultations of Giambattista Morgagni. Edited by Saul Jarcho, MD. 536 pp. Virginia, The University of Virginia Press, 1984. $42.50 (hardcover)

INFECTIOUS DISEASES

Infections: Recognition, Understanding, Treatment. By J. C. Pechère, MD, et al. 606 pp, illustrated. Pennsylvania, Lea & Febiger, 1984. $32.60 (hardcover)

INTERNAL MEDICINE

Aids. The Epidemic of Kaposi's Sarcoma and Opportunistic Infections. Edited by Alvin E. Friedman-Kien, MD and Linda J. Laubenstein, MD. 351 pp, illustrated. New York, Masson Publishing USA, Inc, 1984. $49.50 (hardcover)

Diabetes. The Glucograf Method of Normalizing Blood Sugar. By Richard K. Bernstein, MD. 294 pp, illustrated. California, Jeremy P. Tarcher, Inc, 1984. $8.95 (softcover)

Manual of Antibiotics and Infectious Diseases. By John E. Conte, Jr and Steven L. Barriere. 351 pp, illustrated. Pennsylvania, Lea & Febiger, 1984. $18.50 (paperback Comb-binding)

Practical Strategies in Outpatient Medicine. By Brendan M. Reilly, MD. 832 pp, illustrated. Pennsylvania, WB Saunders Company, 1984. $44.50 (hardcover)

MISCELLANEOUS

Alternatives in Health Care Delivery: Emerging Roles for Physician Assistants. By Reginald D. Carter, PhD, PA, Henry B. Perry, MD, PhD. 388 pp. Missouri, Warren H. Green, Inc, 1984. $42.50 (hardcover)

Exercise for the Chronic Pain Patient. By Mark Muse, Bruce LeFew, Mohammed Shafiei. 104 pp, illustrated. New York, Mouvement Publications, Inc, 1984. $9.95 (paperback)

Health and Healing. Understanding Conventional & Alternative Medicine. By Andrew Weil, MD. 296 pp. Massachusetts, Houghton Mifflin Company, 1983. $13.95 (hardcover)

Making an Issue of Child Abuse. Political Agenda Setting for Social Problems. By Barbara J. Nelson. 169 pp. Illinois, The University of Chicago Press, 1984. $17.50 (hardcover)

Mastering Multiple Sclerosis. Edited by John K. Wold, MD, Steven N. Fellows, Anne E. Tindall-Jones, Robert C. Sheldon, Mitzi Wolf. 330 pp, illustrated. Vermont, Academy Books, 1984. $11.50 (plastic ringbound)

The Problems of Work. How to Solve Them and Succeed. By L. Ron Hubbard. 179 pp. California, Bridge Publications, Inc, 1983. $6.95 (softcover)

NEUROLOGY

Neurologic Problems. Volume 3 of the RN Nursing Assessment Series. By Diana I. Bubb, RN. 248 pp, illustrated. New Jersey, Medical Economics Books, 1984. $10.95 (paperback)

OBSTETRICS AND GYNECOLOGY

Abortion and the Politics of Motherhood. By Kristin Luker. 324 pp, illustrated. California, University of California Press, 1984. $14.95 (hardcover)

Operative Perinatology. Invasive Obstetric Techniques. Edited by Leslie Iffy, MD, David Charles, MD. 1084 pp, illustrated. New York, Macmillan Publishing Co, 1984. $110.00 (hardcover)

OPHTHALMOLOGY

Glaucoma Surgery. By Maurice H. Luntz, MD, Raymond Harrison, MD, Howard I. Schenker, MD. 149 pp, illustrated. Maryland, Williams & Wilkins, 1984. $75.00 (hardcover)

ORTHOPEDICS

Your Aching Back: A Doctor's Guide to Relief. By Augustus A. White III, MD. 288 pp, illustrated. New York, Bantam Books, 1983. $3.95 (paperback)

PEDIATRICS

Selective Nontreatment of Handicapped Newborns. By Robert Weir. 292 pp. New York, Oxford University Press, 1984. $27.95 (hardcover)

PSYCHIATRY

A Child Dies. A Portrait of Family Grief. By Joan Hagan Arnold, Penelope Buschman Gemma. 160 pp, illustrated. Maryland, Aspen Systems Corporation, 1983. $21.50 (hardcover)

RADIOLOGY

Principles and Practices of the College-Based Radiography Program. Edited by O. Gary Lauer, PhD. 280 pp, illustrated. Missouri, Warren H. Green, Inc, 1984. $37.50 (hardcover)

OBITUARIES

In addition to these listings, the Journal *will publish obituaries written by physician readers. Inquiries should first be made to the Editor.*

Arthur F. Anderson, MD, Kennett Square, Pennsylvania. Died March 3, 1984; age 90. Dr Anderson was a 1916 graduate of Tufts University School of Medicine. He was a member of the New York County Medical Society and the Medical Society of the State of New York.

Alfred Alvin Angrist, MD, Bronx. Died March 19, 1984; age 82. He was a 1926 alumnus of the State University of New York Downstate Medical Center. Dr Angrist was a Fellow of the American College of Pathologists and a Diplomate of the American Board of Pathology. His memberships included the Academy of Medicine, the New York Pathological Society, the New York State Society of Pathologists, the American Society for Clinical Investigation, the American Association of Pathologists and Bacteriologists, the International Academy of Pathology, the American Society for Experimental Pathology, the American Society of Clinical Pathologists, the Medical Society of the County of Queens and the Medical Society of the State of New York.

Isamettin Mehmet Aral, MD, Sea Cliff. Died February 16, 1984; age 61. Dr Aral graduated in 1950 from Faculté Francaise de Médecine de la Universitat de St. Joseph, Beyrouth, Syria. He was a Fellow of the American College of Radiology and a Diplomate of the American Board of Radiology. His memberships included the Academy of Medicine, the American Radium Society, the Society of Nuclear Medicine, the Pan American Medical Association, the Nassau County Medical Society and the Medical Society of the State of New York.

William E. Ayling, MD, Syracuse. Died February 6, 1984; age 91. Dr Ayling was an alumnus of State University of New York Upstate Medical Center, graduating in 1918. He was a Diplomate of the American Board of Preventive Medicine, and was a member of the Academy of Medicine, the American Public Health Association, the American School Health Association, the Onondaga County Medical Society and the Medical Society of the State of New York.

Theodore A. Ballien, MD, Albany. Died March 6, 1984; age 70. He was a 1945 alumnus of Hahnemann Medical College and Hospital of Philadelphia. Dr Ballien was a member of the Medical Society of the County of Albany and the Medical Society of the State of New York.

Harry Barowsky, MD, New York. Died December 25, 1983; age 77. He was a 1931 alumnus of New York Medical College, Flower and Fifth Avenue Hospitals. Dr Barowsky was a Fellow of the American College of Gastroenterology and a member of the New York Academy of Gastroenterology, the New York Gastroenterological Society, the American Gastro-Enterological Association, the New York County Medical Society and the Medical Society of the State of New York.

Francis Joseph Buckley, MD, Floral Park. Died February 6, 1984; age 80. Dr Buckley graduated from George Washington University School of Medicine in 1929. His memberships included the Academy of Medicine, the Nassau County Medical Society, and the Medical Society of the State of New York.

John Burke, MD, Buffalo. Died March 2, 1984; age 81. He was a 1928 alumnus of Yale University School of Medicine. Dr Burke was a Fellow of the American College of Surgeons and a Diplomate of the American Board of Surgery. He was a member of the Academy of Medicine, the Medical Society of the County of Erie and the Medical Society of the State of New York.

Raymond Joseph Byron, MD, Schenectady. Died January 24, 1984; age 70. He graduated from Albany Medical College of Union University in 1938. Dr Byron was a member of the American Academy of Family Physicians, the Medical Society of the County of Schenectady, and the Medical Society of the State of New York.

Hyman Colin, MD, Miami, Florida. Died March 2, 1984; age 85. Dr Colin was a 1930 graduate of the State University of New York Downstate Medical Center. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Arthur Niles Curtiss, MD, Syracuse. Died January 24, 1984; age 87. Dr Curtiss graduated from State University of New York Upstate Medical Center in 1923. He was a member of the Academy of Medicine, the Onondaga County Medical Society, and the Medical Society of the State of New York.

Richmond Douglass, MD, Olean. Died February 14, 1984; age 89. Dr Douglass was a 1920 alumnus of Cornell University Medical College. He was a Fellow of the American College of Surgeons and a Diplomate of the American Board of Thoracic Surgery. His memberships included the New York Society for Thoracic Surgery, the American Association for Thoracic Surgery, the American Thoracic Society, the Dutchess County Medical Society and the Medical Society of the State of New York.

Michael Joseph Dunne, MD, Fishkill. Died March 19, 1984; age 84. Dr Dunne was a 1927 alumnus of the National University of Ireland. He was a member of the Nassau County Medical Society and the Medical Society of the State of New York.

Dante Vincent Durante, MD, Rye. Died February 11, 1984; age 78. Dr Durante was a 1935 alumnus of the Stritch School of Medicine of Loyola University and a member of the American Academy of Family Physicians, the Bronx County Medical Society and the Medical Society of the State of New York.

Samuel Julius Ehrlich, MD, Hallandale, Florida. Died March 18, 1984; age 83. Dr Ehrlich was a 1927 graduate of St. Louis University School of Medicine. He was a member of the American Geriatrics Society, the Bronx County Medical Society and the Medical Society of the State of New York.

Martin P. Fischer, MD, Huntington Station. Died January 31, 1984; age 58. He was a 1952 alumnus of the University of Virginia School of Medicine, and a member of the American Psychiatric Association, the Sulfolk County Medical Society, and the Medical Society of the State of New York.

Jacob Phillip Freedman, MD, Rochester. Died August 3, 1983; age 76. He was a 1932 graduate of Tufts University School of Medicine. Dr Freedman was a member of the Medical Society of the County of Monroe and the Medical Society of the State of New York.

David S. Gerbarg, MD, Kingston. Died March 11, 1984; age 60. He was a 1948 graduate of the University of Pennsylvania School of Medicine. Dr Gerbarg was a Fellow of the American College of Physicians, a Fellow of the American College of Gastroenterology and a Diplomate of the American Board of Internal Medicine. He was a member of the New York State Society of Internal Medicine, the Medical Society of the County of Ulster and the Medical Society of the State of New York.

Sidney Gover, MD, New York. Died August 28, 1983; age 75. Dr Gover graduated from Eclectic Medical College, Cincinnati in 1938. He was a member of the New York Medical Society and the Medical Society of the State of New York.

Morris Harry Hadler, MD, Eastchester. Died January 13, 1984; age 80. He was a 1929 graduate of Harvard Medical School. Dr Hadler was a member of the Medical Society of the County of Ulster and the Medical Society of the State of New York.

Albert Hall Harris, MD, Slingerlands. Died February 27, 1984; age 79. Dr Harris was a 1931 alumnus of Harvard Medical School. He was a Fellow of the American College of Preventive Medicine, a Diplomate of the American Board of Preventive Medicine, and a member of the Medical Society of the County of Albany and the Medical Society of the State of New York.

Lawrence Edgar Hummel, MD, Eden. Died March 12, 1984; age 81. He was a 1931 alumnus of Harvard Medical School. Dr Hummel was a Fellow of the American College of Physicians and a Diplomate of the American Board of Internal Medicine. His memberships included the Academy of Medicine, the International Society of Hematology, the Pan American Medical Association, the Medical Society of the County of Erie and the Medical Society of the State of New York.

Eugenia Ingerman, MD, New York. Died February 5, 1984; age 93. An alumnus of Cornell University Medical College, Dr Ingerman graduated in 1916. She was a member of the New York County Medical Society and the Medical Society of the State of New York.

Abraham Jezer, MD, Bronx. Died January 17, 1984; age 79. Dr Jezer was a 1930 graduate of New York University College of Medicine. He was a Fellow of the American College of Chest Physicians, a Diplomate of the American Board of Internal Medicine, and a member of the Academy of Medicine, the Bronx County Medical Society, and the Medical Society of the State of New York.

P. C. Raymond Kaplow, MD, Brooklyn. Died December 4, 1983; age 74. He was a 1935 graduate of New York University College of Medicine. Dr Kaplow was a Qualified Fellow of the International College of Surgeons, a Diplomate of the American Board of Surgery, and a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Angelo Francis Leone, MD, Medina. Died January 28, 1984; age 80. He graduated from the University of Buffalo School of Medicine in 1932, and was a member of the Academy of Medicine, the Medical Society of the County of Orleans and the Medical Society of the State of New York.

Walter Ralph Loewe, MD, New York. Died December 28, 1983; age 89. Dr Loewe attended Tufts University School of Medicine and graduated in 1917. He was a Fellow of the American College of Surgeons, a Fellow of the American College of Angiology, and a Diplomate of the American Board of Ophthalmology. He was a member of the New York Society for Clinical Ophthalmology, the American Academy of Ophthalmology and Otolaryngology, the Pan American Medical Association, the New York County Medical Society and the Medical Society of the State of New York.

Niels Gerhard Madsen, MD, Philadelphia, Pennsylvania. Died January 22, 1984; age 86. He was a 1935 graduate of the University of Buffalo School of Medicine. Dr Madsen was a member of the Medical Society of the County of Monroe and the Medical Society of the State of New York.

Joseph M. F. Malin, MD, Staten Island. Died March 6, 1984; age 77. Dr Malin was a 1932 alumnus of Georgetown University School of Medicine. He was a member of the Richmond County Medical Society and the Medical Society of the State of New York.

Milton John Matzner, MD, Westport, Connecticut. Died October 18, 1983; age 84. He graduated from Columbia University College of Physicians and Surgeons in 1925, and was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

William Francis Meehan, MD, Eastchester. Died September 23, 1983; age 72. Dr Meehan was a 1937 graduate of Jefferson Medical College of Philadephia. His memberships included the Academy of Medicine, the New York State Society of Internal Medicine, the Medical Society of the County of Westchester and the Medical Society of the State of New York.

George Redvers Murphy, MD, Elmira. Died June 2, 1981; age 81. He was a 1924 alumnus of Columbia University College of Physicians and Surgeons. Dr Murphy was a Diplomate of the American Board of Pediatrics and a member of the American Academy of Pediatrics, the Medical Society of the County of Chemung and the Medical Society of the State of New York.

Josef Novak, MD, Greenwich, Connecticut. Died December 29, 1983; age 104. He graduated in 1903 from Deutsche Universitat Medizinische Fakultat, Prague, and was a Diplomate of the American Board of Obstetrics and Gynecology. He was a member of the New York County Medical Society and the Medical Society of the State of New York.

Yusuf Onel, MD, Bronx. Died December 26, 1983; age 55. Dr Onel was a 1954 alumnus of the University of Istanbul Medical Faculty-Istanbul Universitesi Tip Fakultese, and a member of the American Academy of Neurology, the Bronx County Medical Society, and the Medical Society of the State of New York.

Richard Townley Paton, MD, Southampton. Died February 28, 1984; age 83. He was a 1929 graduate of Johns Hopkins University School of Medicine and a Diplomate of the American Board of Ophthalmology. His memberships included the Academy of Medicine, the New York Ophthalmology Society, the American Academy of Ophthalmology and Otolaryngology, the American Ophthalmological Society, Suffolk County Medical Society and the Medical Society of the State of New York.

John Warren Pickren, MD, Buffalo. Died March 24, 1984; age 62. He was a 1944 graduate of the University of Arkansas School of Medicine. Dr Pickren was a Fellow of the American College of Pathologists and a Diplomate of the American Board of Pathology. His memberships included the American Association for Cancer Research, the American Society of Clinical Pathologists, the Medical Society of the County of Erie and the Medical Society of the State of New York.

Michael Pollack, MD, Long Beach. Died March 27, 1984; age 84. He was a 1924 alumnus of Columbia University College of Physicians and Surgeons. Dr Pollack was a member of the American Geriatrics Society, the Medical Society of the County of Queens and the Medical Society of the State of New York.

John Marvin Prutting, MD, New York. Died March 16, 1984; age 73. He was a 1938 graduate of Yale University School of Medicine. Dr Prutting was a member of the New York Cardiological Society, the American Geriatrics Society, the New York County Medical Society and the Medical Society of the State of New York.

Georgia Reid, MD, West Palm Beach, Florida. Died December 21, 1983; page 87. Dr Reid graduated from Cornell University Medical College in 1920. She was a Diplomate of the American Board of Obstetrics and Gynecology, and a member of the American Medical Women's Association, the New York County Medical Society and the Medical Society of the State of New York.

Mary Helen Rowley, MD, Schenectady. Died April 13, 1983; age 68. Dr Rowley was a 1941 alumna of the University of Vermont College of Medicine. She was a member of the Medical Society of the County of Schenectady and the Medical Society of the State of New York.

Jeremiah Edward Ryan, MD, Conklin. Died March 7, 1984; age 73. Dr Ryan was a 1938 graduate of Georgetown University School of Medicine. He was a Diplomate of the American Board of Dermatology, and a member of the Academy of Medicine, the New York State Dermatological Society, the American Academy of Dermatology, Broome County Medical Society, and the Medical Society of the State of New York.

Walter Salmore, MD, Lake Peeksill. Died November 21, 1983; age 80. Dr Salmore was a 1928 graduate of New York Medical College, Flower and Fifth Avenue Hospitals. He was a member of the Bronx County Medical Society and the Medical Society of the State of New York.

Paul Benedice Sheldon, MD, Princeton, New Jersey. Died January 12, 1983; age 89. He was a 1922 graduate of Washington University School of Medicine. Dr Sheldon was a member of the New York County Medical Society and the Medical Society of the State of New York.

Emile Somekh, MD, Great Neck. Died April 20, 1984; age 68. He was a 1937 graduate of the University of Rome. Dr Somekh was a Diplomate of the American Board of Clinical Immunology and Allergy. His memberships included the American Association for Clinical Immunology and Allergy, the International Society of Allergists, the Royal Society of Health of England, the Nassau County Medical Society and the Medical Society of the State of New York.

John Edward Sullivan, MD, New York. Died December 24, 1983; age 83. Dr Sullivan was a 1927 graduate of Columbia University College of Physicians and Surgeons. He was a Diplomate of the American Board of Surgery. His memberships included the New York State Surgical Society, the American Association for the Surgery of Trauma, the Society for Experimental Biology and Medicine, the New York County Medical Society and the Medical Society of the State of New York.

Marion Baldur Sulzberger, MD, San Francisco, California. Died November 24, 1983; age 88. Dr Sulzberger graduated from the Universitat Zurich Medizinische Fakultat in 1926, and was a member of the New York County Medical Society and the Medical Society of the State of New York.

Myron Abner Thompson, MD, Williamsville. Died March 18, 1984; age 91. Dr Thompson was a 1917 graduate of the University of Buffalo School of Medicine. His memberships included the Academy of Medicine, the American Occupational Medical Association, the Medical Society of the County of Erie and the Medical Society of the State of New York.

Joseph G. Vacca, MD, Schenectady. Died February 4, 1984; age 73. He graduated from St. Louis University School of Medicine in 1939. Dr Vacca was a member of the American Academy of Family Physicians, the Medical Society of the County of Schenectady, and the Medical Society of the State of New York.

Louis A. Vendetti, MD, Buffalo. Died February 19, 1984; age 75. Dr Vendetti was a 1933 alumnus of the University of Buffalo School of Medicine and a member of the Medical Society of the County of Erie and the Medical Society of the State of New York.

Joseph Vogel, MD, Longboat Key, Florida. Died February 25, 1984; age 70. Dr Vogel graduated from Laval University Faculty of Medicine, Quebec in 1941. He was a member of the New York County Medical Society and the Medical Society of the State of New York.

Guidelines for authors

ORIGINALITY

The *New York State Journal of Medicine* welcomes research papers and original essays on the practice of medicine, medical education, public health, the history of medicine, medicolegal matters, legislation, ethics, the mass media and socioeconomic issues in health care.

Manuscripts should be prepared according to the "Uniform requirements for manuscripts submitted to biomedical journals" (*NY State J Med* 1983; 83:1089–1094). The requirements were established by the International Committee of Medical Journal Editors, of which the *Journal* is a participating member. These Guidelines are intended to highlight aspects of the *Journal*'s particular style of publication.

A manuscript will be considered for publication if it is original, has not been published previously in whole or in part in either a medical journal or a lay publication, and is not simultaneously under consideration elsewhere. A copy of any possibly duplicative material, such as a reference "in press," should be submitted along with the manuscript.

PREPARATION

An original typewritten or "word-processed" manuscript and two photocopies (to facilitate outside review) are required. If the manuscript is not accepted for publication, the original and one copy will be returned. All figures must be submitted in triplicate. The manuscript should be double-spaced throughout, including references, tables, legends, quotations, and acknowledgments. A separate title page should include the full title of the paper in upper and lower case type, the names of the authors exactly as they should appear in print (including their highest academic degree), an abbreviated title of no greater than 40 spaces for use as a running foot, and the names of all providers of funding for research on which the paper is based. Information on the amount and allocation of funding is optional.

A corresponding author should be designated in the covering letter. Authors should list their title and affiliation at the time they did the work, and, if different, their present affiliation. The addresses and telephone numbers of all authors should be supplied for editorial purposes. All authors of a manuscript are responsible for having read and approved it for submission.

CATEGORIES

Research Papers should be limited to 2,500 words and should include the following sections: Introduction, Methods, Results, Discussion, and References. Multiple subheadings and numbered lists are discouraged. An abstract limited to 150 words should state the reasons for the study, the main findings, and their implications. Statistical evaluations should be described in the Methods section, and the name and affiliation of the statistician should be included in the acknowledgments if this individual is not listed as a coauthor. Reports of experiments involving human subjects must include a description in the Methods section of the informed consent obtained and a statement that the procedures followed were approved by an institutional research review committee. Anonymity of patients must be preserved. Reports of experiments on animals must note which guidelines were followed for the care and use of laboratory animals.

Case Reports should be limited to 1,250 words. Review Articles should not exceed 3,000 words. Commentaries should be between 750 and 1,000 words. Other kinds of original essays should not exceed 2,000 words. A letter of inquiry should be sent to the editor prior to submitting a Review Article or Commentary.

For Research Papers only, scientific measurements should be given in conventional units, with Système Internationale (SI) units in parentheses. Abbreviations and acronyms should be kept to a minimum, and jargon should be avoided. Generic names of drugs should be used instead of brand names.

FIGURES

The submission of color illustrations or slides is discouraged. Only black and white glossy photographic prints or "camera-ready" artwork will be accepted. The *Journal* is unable to provide art services such as the addition of arrows to photographs. A signed consent for publication must accompany photographs in which the patient is identifiable. Illustrations from other publications generally will not be considered. Legends for illustrations should be typed on a separate sheet, and for photomicrographs should include magnification and stain. Each illustration should be lightly marked on the back in pencil with the name of the first author, the number as cited in the text, and an arrow indicating the top. Each set of illustrations should be submitted unmounted in a separate envelope.

Tables should be simple, self-explanatory, and few in number. Each table should be typed double-spaced on a separate sheet.

REFERENCES

References should be limited to the most pertinent. The recommended maximum number of references is 25 for Research Papers and most other original contributions (except lengthier Review Articles), 12 for Commentaries and Case Reports, and six for letters to the editor.

Authors are responsible for the accurate citation of references. Citation of secondary sources is discouraged except where the original reference is unobtainable. Authors may not cite references they have not read, and the use of abstracts as references should be avoided.

References should be indicated in the text by superscript numbers following the name of the author (eg, Smith^2 reported two cases).

The list of references at the end of the article should be typed double-spaced and references should be numbered in the order in which they appear on the text. When there are six or fewer authors, all should be listed; where there are seven or more, the first three should be listed, followed by *et al.* Names of journals should be abbreviated according to *Index Medicus* and underlined.

Sample references:

1. Kepes ER, Thomas P, Vemulapalli K: Methadone and intravenous morphine requirements. *NY State J Med* 1983; 83:925–927.
2. McGuigan JE. Peptic ulcer. In: Petersdorf RG, Adams RD, Braunwald E, Isselbacher KJ, Martin JB, Wilson JD, eds. *Harrison's Principles of Internal Medicine.* New York, McGraw-Hill, 1983, pp 1697–1712.

REVIEW

All manuscripts are reviewed by the editors, and most manuscripts are sent to outside referees. Decisions concerning acceptance, revision, or rejection of a manuscript are usually made within three to six weeks. Every effort will be made to assure prompt publication of an accepted manuscript. A galley proof will be sent to the author for approval prior to publication.

Address correspondence to Alan Blum, MD, Editor, *New York State Journal of Medicine*, P.O. Box 5404, 420 Lakeville Road, Lake Success, NY 11042.

MEDICAL SOCIETY OF THE STATE OF NEW YORK

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Members of the House 422
Reference Committees 426
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Report of the House Committee on Bylaws 429

HOUSE OF DELEGATES

October 14 through 17, 1984
New York Hilton

SCHEDULE of SESSIONS

Sunday, October 14
Opening Session .... 1:00 p.m.

Monday, October 15
Reference Committee Hearings .... 8:30 a.m.–12:30 p.m.
Reference Committee Hearings .... 1:30 p.m.–6:00 p.m.
Reference Committee Hearings .... 8:00 p.m. (to completion)

Tuesday, October 16
Second Session .... 9:00 a.m.
Third Session .... 1:30 p.m.
Fourth Session .... 8:00 p.m. (if necessary)

Wednesday, October 17
Closing Session .... 9:00 a.m.

A guide to the 1984 annual Meeting

Policy-making in The House of Delegates

This section of the New York State Journal of Medicine is a call to the officers, delegates, and members of the Medical Society of the State of New York to attend the 178th Annual Meeting of the Society and the meeting of its House of Delegates; 291 delegates representing 61 county medical societies, 9 district branches, specialty societies, the hospital medical staff section, 12 medical schools, the resident and medical student membership will meet at the Hilton Hotel in New York City on October 14–17, 1984.

The officers, members of the Council and the Board of Trustees, past presidents of the MSSNY, the Commissioner of the New York State Department of Health, and the Past President of the American Medical Association from New York, Gerald D. Dorman, MD, are also official representatives to the House.

Mandated by the Bylaws of the Society, this section lists the names of elected representatives, delegates who are serving on reference committees, and selections of the Nominating Committee for the election of Officers, Councilors, Trustees and AMA Delegates. Also included are the amendments to the Bylaws which will be considered by the House of Delegates.

Since the House of Delegates is the legislative body of the Society, charged with the general management of the State Society and its affairs, members of the Society are urged to use this information to consult with and advise their representatives. Resolutions introduced by representatives bring members' concerns to the attention of the entire Society. Representatives not only have the responsibility to present the views of their constituents, but also to inform them of the actions taken by this governing body. The House of Delegates also formulates policy for the Society. No officer, councilor, board, commission, committee, or employee may initiate any policy unless such policy has been expressly approved by the House of Delegates or by the Council of the Society.

If one were to choose the most important work of the House of Delegates, it would have to be that of the reference committees. Any member of the Medical Society of the State of New York has the right to appear before any reference committee and participate in its deliberations. It is also in the reference committees that people outside of the State Society are asked to give their views. Nonmember physicians, guests or interested observers who wish to express their opinions may, with permission, come before the reference committee and speak to the business of the committee. I strongly urge members to use this forum to express their views.

John L. Clowe, MD, Speaker
House of Delegates

MEDICAL SOCIETY OF THE STATE OF NEW YORK

ORGANIZED 1807

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New York
President

Allison B. Landolt

Westchester
President-Elect

Richard D. Eberle

Onondaga
Past-President

Daniel F. O'Keeffe

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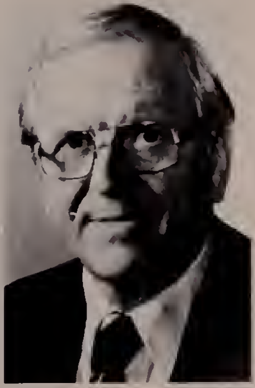

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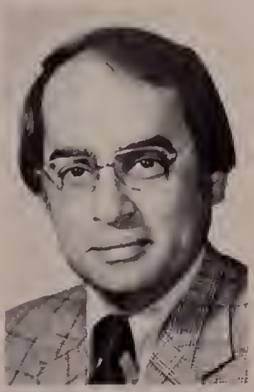

Charles N. Aswad

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Vice-Speaker

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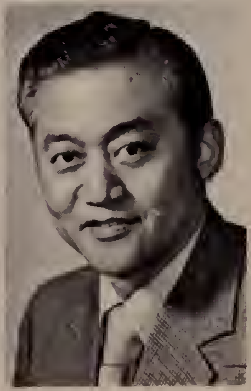
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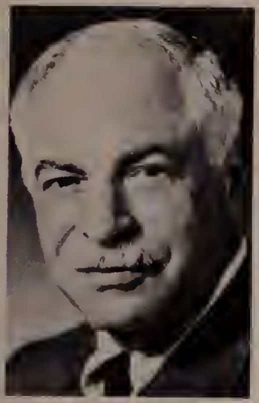

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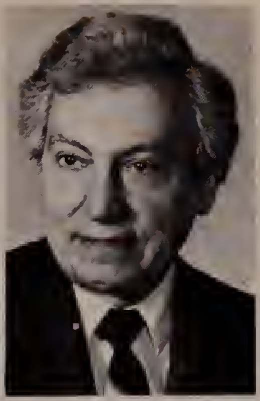
James H. Cosgriff, Jr.

Erie



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Nassau

Richard A. Hughes

Warren

Antonio F. LaSorte

Broome

Frederic W. Holcomb, Jr.

Ulster

Felix Rosenhain

Queens

Robert A. Mayers

Westchester

Stanley A. Steckler

Suffolk

1984 House of Delegates
MEMBERS

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James M. Flanagan, Wayne
George Lim, Oneida
M. Theodore Tanenhaus, Kings

Term Expires 1985
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Samuel M. Gelfand, Nassasu
Richard A. Hughes, Warren
Antonio F. LaSorte, Broome

Term Expires 1986
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Felix R. Rosenhain, Queens
Stanley A. Steckler, Suffolk

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1970–1971—Walter Scott Walls, Erie
1971–1972—George Himler, New York
1972–1973—Edward Siegel, Clinton
1974–1975—Lynn R. Callin, Monroe
1975–1976—Ralph S. Emerson, Nassau
1976–1977—George L. Collins, Jr., Erie
1977–1978—Carl Goldmark, Jr., New York
1978–1979—George T. C. Way, Dutchess
1979–1980—G. Rehmi Denton, Albany
1980–1981—Ralph M. Schwartz, Kings
1981–1982—Milton Rosenberg, Suffolk
1982–1983—Richard D. Eberle, Onondaga

Past President of American Medical Association

Gerald D. Dorman, New York

Commissioner, New York State Department of Health

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(*Elected Delegates of District Branches*)
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Second—Melvyn Bruckstein, Suffolk
Third—Thomas W. Greenlees, Schoharie
Fourth—
Fifth—
Sixth—Vincent I. Maddi, Broome
Seventh—John E. Horn, Steuben
Eighth—Kenneth J. Clark, Orleans
Ninth—Joel E. Mandel, Rockland

Specialty Society Delegates

New York State Society of Anesthesiologists—Joyce M. McChesney, Monroe
New York State Society of Dermatology—Franklin S. Glickman, Kings
New York Chapter—Emergency Physicians—Ralph Altman, New York
New York State Academy of Family Physicians—James R. Nunn, Erie
New York State Society of Internal Medicine—Robert M. Kohn, Erie
New York State Neurosurgical Society—Gerald L. Haines, Schenectady
American College of Obstetricians and Gynecologists—Leonard S. Weiss, Orange
New York State Ophthalmological Society—Francis J. Gilroy, Broome
New York State Society of Orthopaedic Surgeons—John D. States, Monroe
New York State Society of Otolaryngology—Head and Neck Surgery—Fouad B. Michael, Nassau
New York Society of Pathologists—Herbert Lansky, Erie
American Academy of Pediatrics—District II—David Annunziato, Nassau
New York Society of Physical Medicine and Rehabilitation—David Ernstoff, Queens
New York Regional Society of Plastic and Reconstructive Surgery—Phillip R. Casson, New York
New York State Psychiatric Association—Harold E. Berson, Kings
New York State Chapter—Radiology—Robert C. Friedman, Albany
New York State Society of Surgeons—Theodore C. Max, Oneida
New York State Urological Society—Lawrence Ravich, Nassau

Delegates from Component County Medical Societies

Albany (*4*)
- John W. Abbuhl, Albany
- William O'Dwyer, Latham
- Nathan P. Reed, Albany
- Anthony P. Tartaglia, Albany

Allegany (*1*)
- Muhammad Akmal Khan, Wellsville

Bronx (*10*)
- John P. Albanese, Bronx
- Marcos A. Charles, Bronx
- Dattatraya S. Lanjewar, Pelham Manor
- Michael N. Lavacca, Bronx
- Charles Laverdi, Bronx
- Siegfried Mayer, Bronx
- Hugo M. Morales, Bronx
- Govindappa Rangaiah, Scarsdale
- Howard Stanley Schwartz, Bronx
- Juana Toporovsky, Bronx

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- Louis W. Giordano, Endicott
- Theodore R. Poritz, Binghamton
- John F. Spring, Binghamton

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- William C. MacFarland, Olean

Cayuga (*1*)
- Richard J. Freeman, Auburn

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- James G. Dahlie, Jamestown
- Charles R. Sinatra, Jamestown

Chemung (*2*)
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- Gerald P. Schneider, Elmira

Chenango (*1*)
- Norman C. Lyster, Jr., Norwich

Clinton (*1*)
- Robert T. Potter, Plattsburgh

Columbia (1)
- Rosewell D. Shaw, Stottville

Cortland (*1*)
- Nicholas J. Gabriel, Cortland

Delaware (*1*)
- Glen Joshpe, Stamford

Dutchess (*4*)
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- Stephen R. Chernay, Fishkill
- Arthur W. Menken, Poughkeepsie
- Seymour R. Stall, Poughkeepsie

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- Robert A. Caputi, Buffalo
- Anthony J. Federico, Buffalo
- George W. Fugitt, Tonawanda
- Allen L. Lesswing, Buffalo
- Milford C. Maloney, Buffalo
- Leo E. Manning, Amherst
- James F. Phillips, Jr., Buffalo
- Joseph A. Prezio, Buffalo

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Franklin (*1*)
- Alfred A. Hartmann, Sr., Malone

Fulton (*1*)

Genesee (*1*)
- Alfred L. George, Batavia

Greene (*1*)
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Herkimer (*1*)
- Krishna K. Vadlamudi, Ilion

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- Eugene M. Renzi, Watertown

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- Grace A. Altenau, Brooklyn
- Norman S. Blackman, Brooklyn
- Randall D. Bloomfield, Brooklyn
- Joseph R. Brennan, Brooklyn
- Matthew Brody, Brooklyn
- George W. Calvosa, Brooklyn
- Vernal G. Cave, Brooklyn
- Duncan W. Clark, Brooklyn
- Philip Cohen, Brooklyn
- Vashti R. C. Curlin, Brooklyn
- Paul Finkelstein, Brooklyn
- Stanley I. Fishman, Brooklyn
- Robert E. Gordon, Brooklyn
- A. W. Martin Marino, Jr., Brooklyn
- Martin Markowitz, Brooklyn
- Bentley D. Merrim, Brooklyn
- Leo J. Swirsky, Brooklyn
- Vincent Tricomi, Brooklyn

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John C. Herrman, Lowville

Livingston (*1*)
Sheppard Arluck, Geneseo

Madison (*1*)
Leonard A. Argentine, Oneida

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Warren Glaser, Rochester
Nathaniel J. Hurst, Rochester
William A. Kern, Jr., Rochester
Vito Pasqual Laglia, Rochester
Mario B. LoMonaco, Rochester
Charles R. Salamone, Rochester

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Feori F. Pipito, Amsterdam

Nassau (*11*)
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Ray S. Crampton, Syosset
Morton Goldfarb, Massapequa Park
Paul C. Lehmuller, Levittown
Alfred W. Marks, Rockville Centre
Sidney Mishkin, Fort Salonga
Felix A. Monaco, Rockville Centre
John A. Ostuni, Freeport
Henry S. Partridge, Freeport
Patricia G. Squillace, Rockville Centre
Jerome Zwanger, Massapequa

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Melvin H. Becker, Manhasset
Robert S. Bernstein, New York
Irwin J. Cohen, New York
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Hugh Clark Davidson, New York
Wilbur J. Gould, New York
George Hyams, New York
Virginia Kanick, New York
Vance Lauderdale, Jr., New York
Samuel H. Madell, New York
Aaron G. Meislin, New York
George W. Melcher, Jr., New York
Richard B. Nolan, New York
Donna B. O'Hare, New York
Stuart I. Orsher, New York
Richard N. Pierson, Jr., New York
William B. Rawls, Pleasant Valley
Isadore Rosenfeld, New York
Albert M. Schwartz, New York
Miriam Z. Seborer, New York
Clifford L. Spingarn, New York
Meyer Texon, New York

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James J. Kropelin, Niagara Falls
Clark G. Triftshauser, Lewiston

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Gerald C. Gant, New Hartford
Robert M. George, Utica

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David L. Poushter, Syracuse
John T. Prior, Syracuse
George P. Tilley, Syracuse

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Kenneth T. Steadman, Geneva

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Stanley F. Brunn, Port Jervis
Stanley L. Grossman, Newburgh
Jack Manpel, New Windsor
Ansel R. Marks, Middletown

Orleans (*1*)
David B. L. Meza, III, Albion

Oswego (*1*)
James F. Grant, Oswego

Otsego (*1*)
Rodman D. Carter, Cooperstown

Putnam (*1*)
Hari P. Chakravorty, Mahopac

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Robert M. Farrell, Flushing
Fred N. Flatau, Flushing
Irving G. Frohman, Rockaway Beach
Leo Arthur Green, Jackson Heights
Victor Guarneri, Bayside
Edith Gutman, Beechhurst
Nicetas H. Kuo, Flushing
Morton M. Kurtz, Flushing
Hilda Ratner, Beechhurst
Morton M. Safran, Jamaica
Ralph E. Schlossman, South Ozone Park
Lester R. Tuchman, Cos Cob, Connecticut
Ezra A. Wolff, Manhasset

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Melvin Shuter, Islip Terrace

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Wendell L. Bryce, Ithaca
E. James Fogel, Jr., Ithaca

Ulster (*2*)
Joseph B. Basile, Kingston
John A. Cooke, Jr., Kingston

Warren (*2*)
David G. LaPointe, Glens Falls
Larry J. Greenberg, Glens Falls

Washington (*1*)
Arnold B. Wise, Cambridge

Wayne (*1*)
Norman R. Loomis, Ontario

Westchester (*9*)
William P. Clark, Eastchester
Edwin I. Cleveland, Bronxville
Richard L. Fenton, Tarrytown
Armond V. Mascia, Tarrytown
Stanley M. Mendelowitz, Tarrytown
Richard L. Petrillo, Mount Vernon
John A. Ramsdell, White Plains
Thomas Dignan Rizzo, Bronxville
Michael Sierp, Yonkers

Wyoming (*1*)
Stuart L. Dorfman, Arcade

Yates (*1*)
William Dean, Jr., Penn Yan

Medical School Delegates — 12
Albany Medical College of Union University—Samuel S. Ciccio, Albany
Albert Einstein College of Medicine—
Columbia University College of Physicians and Surgeons—Linda D. Lewis, New York
Cornell University Medical College—Jack Richard, New York
Mount Sinai School of Medicine—Sherman Kupfer, New York
New York Medical College—Saverio S. Bentivegna, New York
New York University School of Medicine—Stanford Wessler, New York
State University of New York at Buffalo—Ross Markello, Erie
State University of New York Downstate Medical Center—Schuyler George Kohl, Kings
State University of New York at Stony Brook—Tamarath Knigin Yolles, Suffolk
State University of New York at Syracuse—George F. Reed, Onondaga
University of Rochester School of Medicine and Dentistry—Thomas E. Cardillo, Monroe

Medical Student Delegates — 3
Jefferson J. Katims, Westchester
Robert James Newborn, Albany
Elizabeth Anne Prezio, Onondaga

Resident Membership Delegate — 1
Eugene J. Kalmuk, Jr., Erie

Hospital Medical Staff Delegate — 1

REFERENCE COMMITTEES

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Anthony J. Federico, Erie
Vincent I. Maddi, Broome
Stanley M. Mendelowitz, Westchester
Charles R. Salamone, Monroe

ANNUAL REPORTS REFERRED TO COMMITTEE:

President
President-Elect
Secretary
Treasurer
Board of Trustees
Budget and Finance
Executive Vice-President
New York Delegation to the AMA
District Branches
Physicians' Home
Research and Development
Résumé of Instructions from the 1983 House of Delegates
  Ad Hoc Committee to Study the Feasibility of Relocating MSSNY Headquarters
  Ad Hoc Committee on Physician/Patient Concerns

Bylaws

Stanley A. Steckler, Suffolk, *Chairman*
Victorino Anllo, Erie
Dattatraya G. Lanjewar, The Bronx
James R. Nunn, Erie
Nathan P. Reed, Albany

ANNUAL REPORT REFFERED TO COMMITTEE:

Résumé of Instructions from the 1983 House of Delegates

Medical Services "A"

Hugh Clark Davidson, New York, *Chairman*
John P. Albanese, The Bronx
Donald L. Brooks, Jr., Chemung
Nathaniel J. Hurst, Monroe
Robert T. Potter, Clinton

ANNUAL REPORTS REFERRED TO COMMITTEE:

Alternative Health Care Delivery Systems
Health Planning
Interspecialty
Peer Review
Social Security Administration Disability Benefits Program, Committee to Monitor and Provide Input Into
Workers' Compensation and Occupational Health
Résumé of Instructions from the 1983 House of Delegates
  Ad Hoc Committee to Review Applications From Specialty Societies Seeking Representation in the MSSNY House of Delegates

Medical Services "B"

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Melvin H. Becker, New York
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ANNUAL REPORTS REFERRED TO COMMITTEE:

Health Manpower (Including Nursing and Paramedical Personnel)
Hospital and Professional Relations
Medicaid
Medical Care Insurance
Résumé of Instructions from the 1983 House of Delegates
  Ad Hoc Committee on the Concept of Usual, Customary, and Reasonable Fees

Governmental Affairs and Legal Matters

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Linda Lewis, New York
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* Robert Newborn, Albany
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ANNUAL REPORTS REFERRED TO COMMITTEE:

Ethics
Judicial Council
Legislation
New York State Association of the Professions
Professional Medical Liability Insurance and Defense Board
Résumé of Instructions from the 1983 House of Delegates
  Ad Hoc Committee on the Position of Assisting County Medical Societies in Quashing Subpeonas From the Board for Professional Medical Conduct

Membership Benefits, Publications, and Miscellaneous

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Steven R. Chernay, Dutchess
Roberts J. Silich, Richmond
John D. States, Monroe
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NOMINATING COMMITTEE

To the House of Delegates, Ladies and Gentlemen:

In accordance with Article XI, Section 2 of the Bylaws of the Medical Society of the State of New York, the Nominating Committee met at the Society's headquarters, 420 Lakeville Road, Lake Success, New York, on Thursday, May 24, 1984, at 11:00 a.m.

Members of the committee present were:
Member-at-Large—**Richard D. Eberle, M.D.**, Onondaga, *Chairman*
First District Branch—**Edgar P. Berry, M.D.**, New York
Second District Branch—**Stanley A. Steckler, M.D.**, Suffolk
Third District Branch—**Louis G. Jakovic, M.D.**, Albany
Fourth District Branch—**Richard A. Hughes, M.D.**, Warren
Fifth District Branch—**Robert M. George, M.D.**, Oneida
Sixth District Branch—**Paul M. DeLuca, M.D.**, Broome
Seventh District Branch—**James M. Flanagan, M.D.**, Wayne
Eighth District Branch—**Joseph A. Prezio, M.D.**, Erie
Ninth District Branch—**Seymour R. Stall, M.D.**, Dutchess
Member-at-Large—**Ralph M. Schwartz, M.D.**, Kings

After careful consideration of the recommendations submitted by the district branches, county medical societies and the resident and student membership in response to a memorandum, dated January 18, 1984, and nominations from the floor, your committee respectfully nominated the following candidates for election on October 17, 1984:

President—**Allison B. Landolt, M.D.**, Westchester
President-Elect—**Daniel F. O'Keeffe, M.D.**, Warren
Vice-President—**John A. Finkbeiner, M.D.**, New York
Secretary—**John H. Carter, M.D.**, Albany
Assistant Secretary—**George Lim, M.D.**, Oneida
Treasurer—**Charles D. Sherman, Jr., M.D.**, Monroe
Assistant Treasurer—**Morton Kurtz, M.D.**, Queens
Speaker—**John L. Clowe, M.D.**, Schenectady
Vice-Speaker—**Charles N. Aswad, M.D.**, Broome
Trustees (*two for five years*)—**Joseph F. Shanaphy, M.D.**, Richmond
Victor J. Tofany, M.D., Monroe
Councilors (*four for three years*)—**David M. Benford, M.D.**, New York
Duane M. Cady, M.D., Onondaga
James M. Flanagan, M.D., Wayne
M. Theodore Tanenhaus, M.D., Kings

Delegates to the American Medical Association for two years commencing January 1, 1985:
Charles N. Aswad, M.D., Broome
Edgar P. Berry, M.D., New York
William P. Clark, M.D., Westchester
John L. Clowe, M.D., Schenectady
Hugh C. Davidson, Jr., M.D., New York
Richard D. Eberle, M.D., Onondaga
Robert E. Gordon, M.D., Kings
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James J. Kropelin, M.D., Niagara
Dattatraya G. Lanjewar, M.D., The Bronx
Robert A. Mayers, M.D., Westchester
Richard N. Pierson, Jr., M.D., New York
Milton Rosenberg, M.D., Suffolk
Felix R. Rosenhain, M.D., Queens
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Ralph M. Schwartz, M.D., Kings
Joseph F. Shanaphy, M.D., Richmond
Jeffrey Spitzer, M.D., Albany
Stanley A. Steckler, M.D., Suffolk
George T. C. Way, M.D., Dutchess

The ten nominees receiving the largest number of votes will be delegates; the second ten will be alternates.

Respectfully submitted,
Richard D. Eberle, M.D., *Chairman*

HOUSE COMMITTEE ON BYLAWS

To the House of Delegates, Ladies and Gentlemen:

The members of the House Committee on Bylaws are as follows:

George Lim, M.D., *Chairman*	Oneida
Edgar P. Berry, M.D.	New York
Robert Kohn, M.D.	Erie
Allison B. Landolt, M.D.	Westchester
Sidney Mishkin, M.D.	Nassau
Daniel F. O'Keeffe, M.D.	Warren
Seymour Stall, M.D.	Dutchess
Stanley Steckler, M.D.	Suffolk
Bernard J. Pisani, M.D., *President, ex officio*	New York
Victor J. Tofany, M.D., *Secretary, ex officio*	Monroe
John L. Clowe, M.D., *Speaker, ex officio*	Schenectady
Milton Rosenberg, M.D., *Executive Vice-President, ex-officio*	
Donald R. Moy., J.D., *General Counsel, ex-officio*	

A meeting of the Reference Committee on Bylaws was held at the Concord Hotel, Kiamesha Lake, New York on October 29, 1983. The Reference Committee was appointed to receive input from delegates as to their thoughts on the resolutions referred to the House Committee on Bylaws. The input received from the meeting of the Reference Committee on Bylaws proved to be of great assistance to the House Committee on Bylaws.

In all, four resolutions asking for amendments to the Bylaws were referred to the Committee for its consideration.

The following actions were taken with respect to the resolutions referred to this Committee:

Resolution 83-1, Resident Membership Bylaws

Introduced by Edward Siegel, M.D., as an Individual

Whereas, The House of Delegates of the Medical Society of the State of New York created a resident membership class of the MSSNY; and

Whereas, Article II, Section 1, paragraphs 9 and 10; Article II, Section 2, paragraph 5; and Article XVIII, Section 2, paragraphs 5 and 6, of the Bylaws of the MSSNY provide for and define this resident membership class; and

Whereas, In accordance with these provisions, the resident membership of the MSSNY is now about 600; and

Whereas, The resident members should be permitted to organize under their own bylaws, subject to the Bylaws of the MSSNY, and to hold an annual business meeting of the resident membership prior to the annual meeting of this House of Delegates; therefore be it

Resolved, That the Bylaws of the Medical Society of the State of New York be amended to enable the resident membership to adopt bylaws to govern its internal affairs, provided that such bylaws are not in conflict with the Bylaws of the MSSNY and are approved by the Council; and be it further

Resolved, That Article II, Section 1, of the Bylaws of the MSSNY be amended by adding paragraph 11 to read as follows: (additions italicized)

"*The resident membership shall be permitted to adopt bylaws to govern its internal affairs, and hold an annual business meeting. Such bylaws shall not be in conflict with the Bylaws of the Medical Society of the State of New York and must be approved by the Council to become effective.*"

The Committee believes that the adoption of bylaws and an annual business meeting of the resident membership is necessary for the resident membership to regulate its internal affairs. The Committee is also of the opinion that this could be instrumental in involving the resident membership in organized medicine.

The Committee recommends **APPROVAL** of Resolution 83-1.

Resolution 83-2, Delegate Representation in the House of Delegates

Introduced by Edward Siegel, M.D., as an Individual

Whereas, For 139 years representation to the House of Delegates of the Medical Society of the State of New York rested on political divisions within the State; from 1807 to 1898 it followed the lines of senatorial districts and from 1898 to 1946 representation was based on the number of assembly districts contained in each judicial district of the State; and

Whereas, In 1946 the Bylaws of the Medical Society of the State of New York were changed to allow for a more equitable distribution of delegates; county medical societies were allowed to determine delegate allocation by one of two optional methods —

1. entitlement to as many delegates as there are State assembly districts in such county; and
2. based on the number of members belonging to such county medical society; and

Whereas, At the present time thirty-one assembly districts cross county lines; in some instances an assembly district is divided among four and five counties; and

Whereas, At this meeting of the House of Delegates representation from seven county medical societies is based on the number of assembly districts in their county, and if their allocation were based on membership some would be entitled to a much smaller number of delegate representatives; and

Whereas, There is no rational correlation between the number of assembly districts in a county to the number of members in a county medical society; and

Whereas, In a membership organization representation to the governing body of the Society should be equitable and be based on proportional membership; therefore be it

Resolved, That Article III, Section 1, paragraph 2 of the Bylaws of the Medical Society of the State of New York be amended to read as follows: (Deletions in brackets)

[The number of delegates to which each component county medical society is entitled shall be determined by one of the two following methods:]

[a. Each component county medical society shall be entitled to as many delegates as there shall be State assembly districts in such county at the time of election, but each county medical society shall be entitled to elect at least 1 delegate;]

b. Any component county medical society, which according to the rolls of the Medical Society of the State of New York two months prior to the annual meeting, shall have had up to 99 members, shall be entitled to 1 delegate. Any component county medical society having 100 to 199 members shall be entitled to 2 delegates. Any component county medical society having 200 to 349 members shall be entitled to 3 delegates. Any component county medical society having 350 to 499 members shall be entitled to 4 delegates. Any component county medical society having 500 to 749 members shall be entitled to 5 delegates. Any component county medical society having 750 to 999 members shall be entitled to 6 delegates. Any component county medical society having 1,000 or more members shall be entitled to at least 7 delegates and 1 additional delegate for each additional 300 members. Each component county medical society shall be entitled to designate at least 1 delegate, but no component county medical society shall be entitled to designate more than 30 delegates.

Under the present Bylaws, county medical societies have an option on which to base their delegate representation. This option has been followed for the past 40 years. After a thorough review, the Committee does not feel that there is sufficient cause to discontinue this methodology.

The Committee, therefore, recommends **DISAPPROVAL** of Resolution 83-2.

Resolution 83-6, Life Membership

Introduced by First District Branch

Whereas, The present policy for life membership has worked unexpected financial hardship on component county medical societies, as well as the Medical Society of the State of New York; therefore be it

Resolved, That Article II, Section 1, paragraph 6 of the Bylaws of the Medical Society of the State of New York be amended as follows: (additions italicized, deletions in brackets)

"An active member in good standing who has completely withdrawn from the active practice of medicine and who has been a member in good standing for the ten consecutive years prior [to the age of sixty-five years] *to the attainment of the age of seventy-two years* or an active member in good standing who continues *in* the active practice of medicine and who has been a member in good standing for the ten consecutive years prior to the attainment of the age of seventy years, or an active member in good standing for ten consecutive years or more who is permanently disabled, may apply for life membership. The House of Delegates or the Council may waive the requirements in a proper case where there appear to be extenuating circumstances. He shall apply for such life membership to the component county medical society of which he is a member. His application shall be governed by the constitution and bylaws of the component county medical society relative to active membership."

PAST HOUSE ACTION: Resolution 79-39

After a thorough review, the Committee voted to amend this resolution by deleting the phrase "to the age of sixty-five years" and inserting the phrase "to the attainment of the age of sixty-seven years". The resolve would then read: (additions italicized, deletions in brackets)

"An active member in good standing who has completely withdrawn from the active practice of medicine and who has been a member in good standing for ten consecutive years prior [to the age of sixty-five years] *to the attainment of the age of sixty-seven years* or an active member in good standing who continues *in* the active practice of medicine and who has been a member in good standing for the ten consecutive years prior to the attainment of the age of [seventy] *seventy-two* years, or an active member in good standing for ten consecutive years or more who is permanently disabled, may apply for life membership. The House of Delegates or the Council may waive the requirements in a proper case where there appear to be extenuating circumstances. He shall apply for such life membership to the component county medical society of which he is a member. His application shall be governed by the constitution and bylaws of the component county medical society relative to active membership."

It is the opinion of the Committee that this resolution, as amended, is appropriate for the fiscal and administrative integrity of the Medical Society of the State of New York.

The Committee recommends **APPROVAL** of Resolution 83-6, as amended.

At the request of the committee, MSSNY staff has prepared the following specific information on the fiscal impact of this resolution as it affects the MSSNY as a whole, and by implication, how it affects each county medical society.

RESOLUTION 83-6
LIFE MEMBERSHIP

In accordance with the request of the House Committee on Bylaws, the following age analysis of the members of the Medical Society of the State of New York, excluding life members, is provided:

	AGE	MALE	FEMALE
Under 25		14	
	25	1	1
	26	8	1
	27	12	3
	28	33	11
	29	59	19
	30	121	31
	31	189	34

AGE	MALE	FEMALE
32	279	41
33	347	43
34	373	43
35	373	55
36	425	48
37	474	51
38	442	52
39	449	31
40	415	38
41	501	64
42	485	55
43	499	64
44	485	53
45	475	51
46	513	56
47	584	63
48	510	42
49	551	46
50	557	52
51	583	50
52	580	45
53	594	43
54	576	38
55	597	44
56	588	37
57	604	48
58	508	55
59	480	47
60	515	51
61	470	38
62	406	36
63	437	35
64	401	28
65	348	30
66	320	34
67	282	17
68	271	20
69	270	28
70	265	26
71	150	8
72	77	9
73	68	8
74	56	7
75	66	5
76	29	2
77	14	4
78	8	2
79	2	
80	6	
81	1	1
82		
Above 82	7	

TOTAL = 20,597*

Average Age of MSSNY Members = 50.49

These figures indicate that out of 20,597 dues paying members, 4,858, or approximately 25%, are sixty years of age or older.

The numbers indicate that a potential financial problem exists due to the large number of members who are at or near the retirement age. While it is not possible to exactly predict what financial impact the proposed resolution amended and approved by the House Committee on Bylaws will effect, the analysis below provides the savings that the Bylaws amendment could bring in the first year.

In calendar year 1984, in order to qualify for life membership, an active member either had to have completely retired from the active practice of medicine and had been a member in good standing for the ten consecutive years prior to the age of 65, or, assuming the individual continued the active practice of medicine, the active member had to be in good standing for the ten consecutive years prior to the age of 70. Based on these requirements, the MSSNY Membership Division reported that in 1984, of the members who were at least 65 years of age, 6% applied for and were granted life membership on the basis of the complete withdrawal from the active practice of medicine.[†] Assuming the Bylaws are amended so that 67 years of age replaces 65 years of age, members who are currently between the ages of 64 and 65 (total 807 members) will not qualify for life membership. These members could otherwise qualify for life membership in 1985 if the Bylaws are not amended. Assuming further that the 6% election rate were to remain constant in 1985, the following savings can be realized from the stricter requirement:

807 × .06 = 48 members
×
$225.00 = $10,800.00

Assuming that 72 years of age replaces 70 years of age, the members who are currently between the ages of 69 and 70 (589 members) would not qualify for life membership if they continue the active practice of medicine. These members would otherwise qualify for life membership without regard to the practice of medicine if the Bylaws are not amended. The MSSNY Membership Division has reported that in 1984, of the members who were 70 years of age or older, 30% applied for and were granted life membership.[†] Assuming further that the 30% were to remain constant in 1985, the following savings could be realized:

589 × .30 = 177 members
×
$225.00 = $39,825.00

Total: $10,800.00
39,825.00
$50,625.00

It should be realized that the above only indicates the projected savings in the first year. Similar savings for future years can be projected by applying the age analysis table to the rate of life membership election (assuming such rate remains constant).

At the same time, savings can be projected by each county medical society by applying the age analysis table as it relates to the individual county medical society.

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* These figures are as of April 27, 1984.

Although not provided in this report, a computer printout is available which indicates the age analysis for each county medical society.

[†] as of May 1, 1984

Resolution 83-10, Medical Student Membership Requirements

Introduced by Andrew Ku, Robert Newborn, and Elizabeth Anne Prezio, Medical Student Delegates

Whereas, Medical student membership in the MSSNY is currently limited to students enrolled in accredited medical and osteopathic schools in New York State; and

Whereas, Each year the MSSNY receives requests for membership from students who live in New York but attend medical school elsewhere in the country; and

Whereas, Many of these students indicate that they wish to establish a relationship with organized medicine in New York State because they plan to return here after medical school; therefore be it

Resolved, That Article II, Section 1, paragraph 4 of the MSSNY Bylaws be amended as follows: (additions italicized, deletions in brackets)

"Student members shall be those members enrolled in recognized medical or osteopathic schools in the [State of New York] *United States* who are pursuing a course of study leading to the degree of Doctor of Medicine or Doctor of Osteopathy, *and who attend medical school or maintain a residence in New York State*. [Eligible students may become members of the Medical Society of the State of New York.] Concurrent membership in a component county medical society and the American Medical Association is not a requirement for student membership. They shall apply for student membership on a form supplied by the secretary together with such dues as are fixed by the House of Delegates. When a student member ceases to be enrolled in a recognized school of medicine or school of osteopathy [in the State of New York] pursuing a course of study leading to a degree of Doctor of Medicine or Doctor of Osteopathy, other than by reason of graduation, he shall be considered to have resigned from membership in the Medical Society of the State of New York."

In the opinion of the Committee, this resolution would not profoundly affect the structure of membership, but would expand eligibility for membership in the MSSNY to a limited number of additional medical students.

The Committee recommends **APPROVAL** of Resolution 83-10.

Your chairman would like to thank, in addition to the members of the Committee and the physicians who testified before it, those members of staff who have greatly helped this Committee; Donald R. Moy, J.D., General Counsel, Ms. Julie Pichardo, Legal Assistant, and Mrs. Joan Grimm for her secretarial assistance to the Committee.

Respectfully submitted,

George Lim, M.D. *Chairman*

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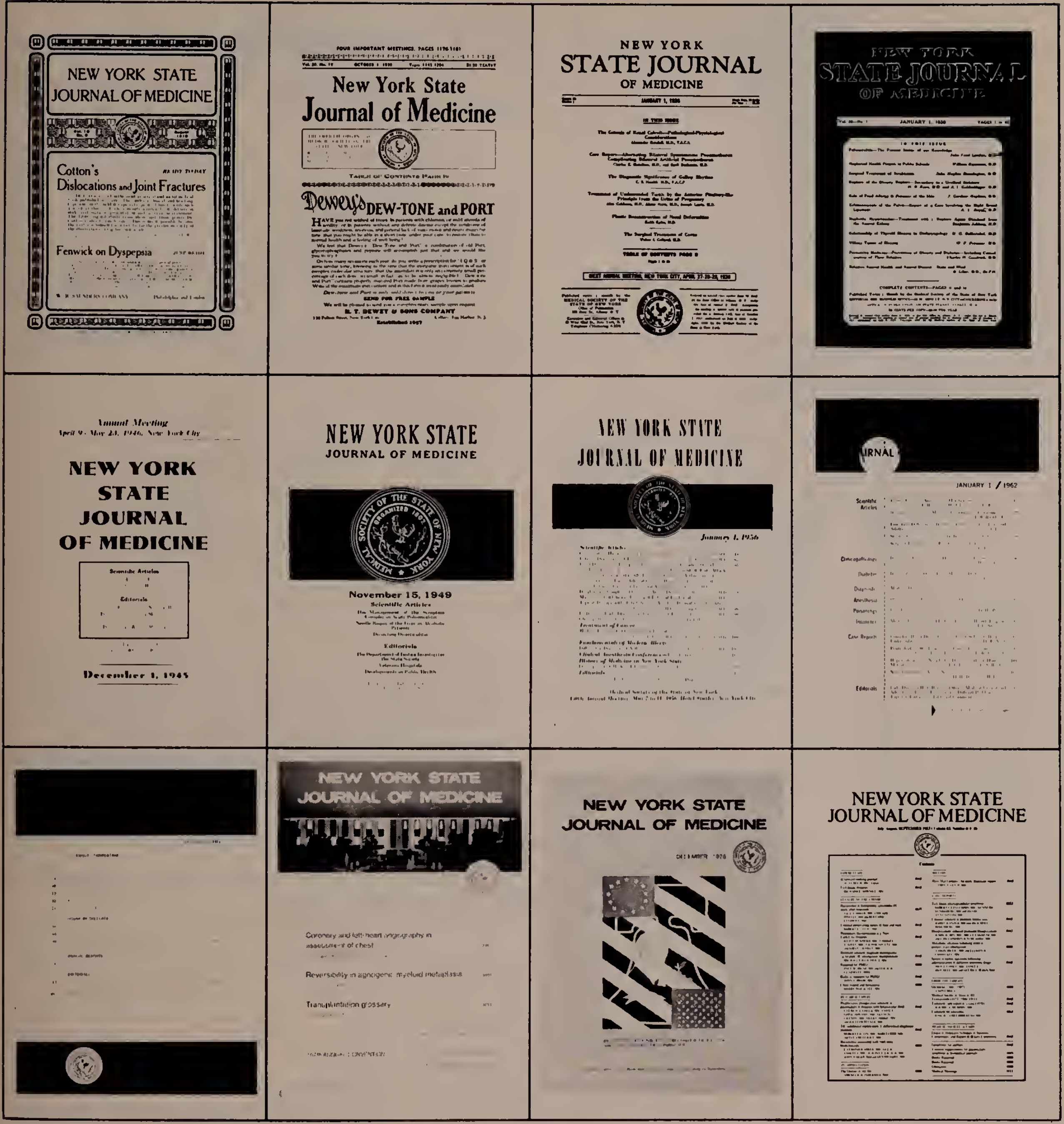
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ALBANY

Sept 16. **Medical Professional Liability and Risk Prevention Education Seminar.** 6 Cat 1 credits. Albany. Info: Medical Quadrangle, Inc, PO Box 368, 318 Bedford Road, Bedford Hills, NY 10507. Tel: (914) 666-0170 or (212) 829-3654.

BROOME

Sept 19. **8th Annual Gerhard A. Krembs Memorial Cardiac Teaching Day.** 4 Cat 1 credits. Binghamton. Info: Sandy Cook, CME Coordinator, Binghamton General Hospital, Mitchell Ave, Binghamton, NY 13903. Tel: (607) 771-2549.

MONROE

Sept 27. **"Help for Today, Hope for Tomorrow" Diabetes Mellitus Management and Research Update.** 6 Cat 1 credits. Rochester. Info: Lorraine Palmer Jost, American Diabetes Association, Hotel Syracuse, Ste 1137, PO Box 1037, Syracuse, NY 13202. Tel: (315) 472-9111.

OSWEGO

Sept 29. **Current Concepts in Medicine—1984.** 5 Cat 1 credits. Oswego. Info: Michael S. Nupuf, MD, 70 West Oneida St, Oswego, NY 13126. Tel: (315) 343-2151.

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Sept 8–9. **Head and Neck Radiology: Advanced Techniques in Diagnostic Imaging.** 12 Cat 1 credits. *Sept 10–14.* **Clinical Magnetic Resonance Imaging.** 30½ Cat 1 credits. San Francisco. Info: University of California School of Medicine, San Francisco, CA. Tel: (415) 666-5731.

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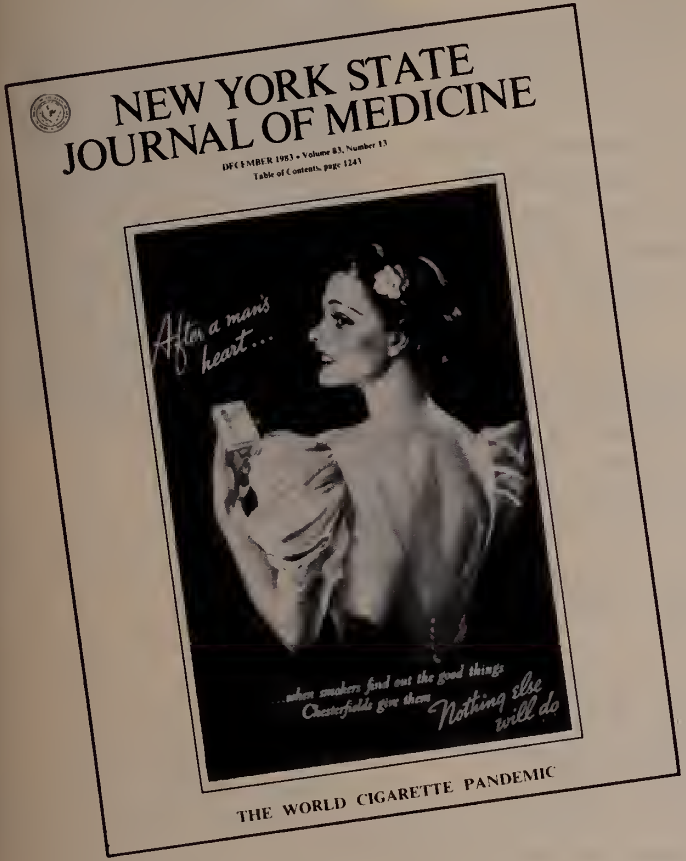
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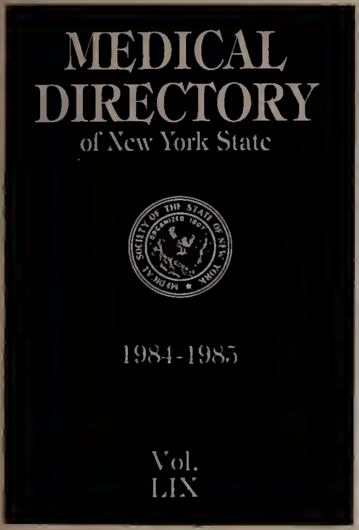

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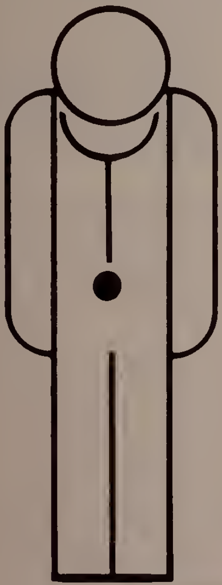

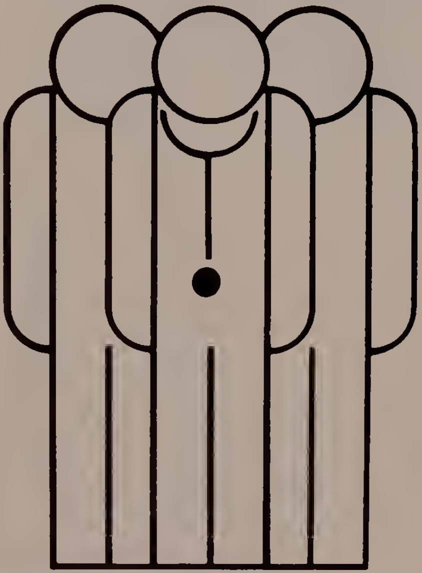

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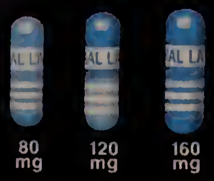

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The mechanism of the antihypertensive effect of INDERAL has not been established Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain.

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension, it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic INDERAL LA is not indicated in the management of hypertensive emergencies

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CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL

WARNINGS. CARDIAC FAILURE Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

> IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e g , dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers

DIABETES AND HYPOGLYCEMIA Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker In one case this resulted after an initial dose of 5 mg propranolol

PRECAUTIONS. *General:* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DRUG INTERACTIONS. Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. INDERAL is excreted in human milk Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia, congestive heart failure; intensification of AV block, hypotension; paresthesia of hands; thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System. lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Auto-Immune. In extremely rare instances, systemic lupus erythematosus has been reported

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved The usual maintenance dosage is 120 to 160 mg once daily In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized* The initial oral dose is 80 mg INDERAL LA once daily The usual effective dose range is 160-240 mg once daily The dosage may be increased gradually to achieve optimum migraine prophylaxis If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use

*The appearance of INDERAL LA capsules is a registered trademark of Ayerst Laboratories

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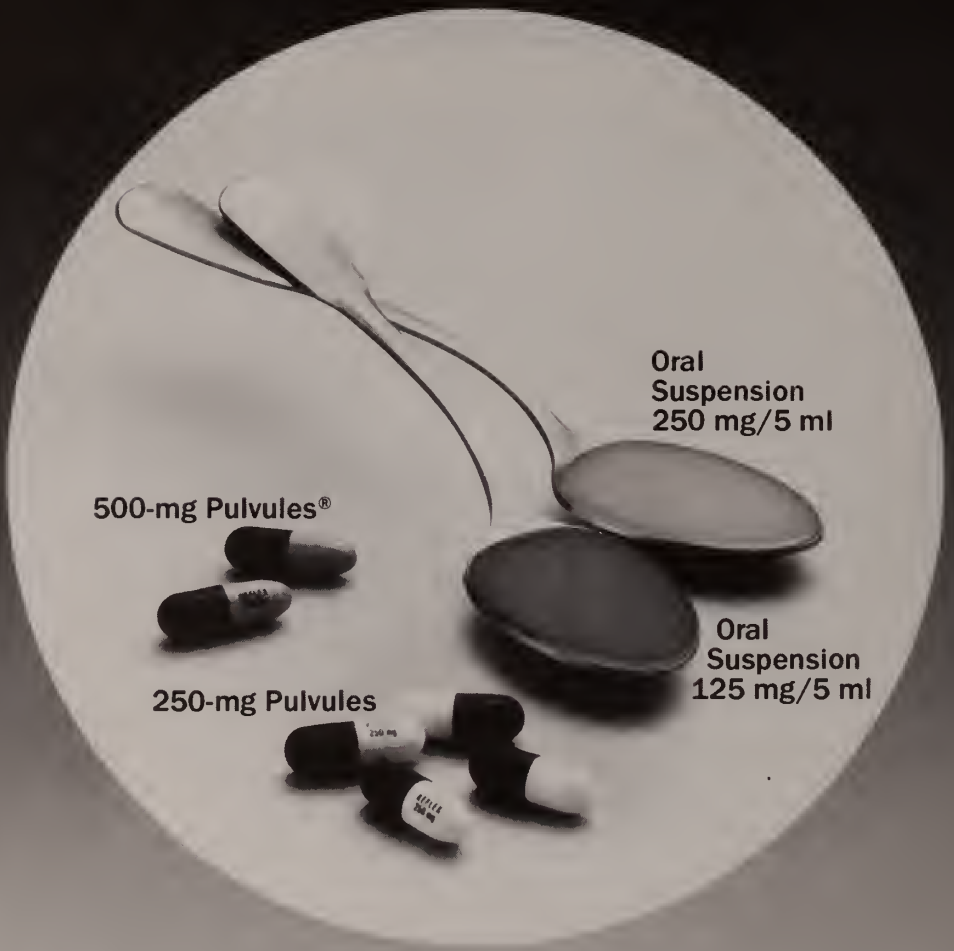

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*Cardizem is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

References:

1. Strauss WE, McIntyre KM, Parisi AF, et al: Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris: Report of a cooperative clinical trial. Am J Cardiol 49:560-566, 1982.
2. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. Chest 78 (July suppl):234-238, 1980.

Reduces angina attack frequency*
42% to 46% decrease reported in multicenter study.[1]

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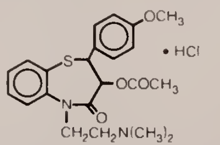
PROFESSIONAL USE INFORMATION

cardizem®
(diltiazem HCl)
30 mg and 60 mg tablets

DESCRIPTION

CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+)-cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem hydrochloride for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina. CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIONS and ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS).

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%), AV block (1.1%). In addition, the following events were reported infrequently (less than 1%) with the order of presentation corresponding to the relative frequency of occurrence.

Cardiovascular:	Flushing, arrhythmia, hypotension, bradycardia, palpitations, congestive heart failure, syncope.
Nervous System:	Paresthesia, nervousness, somnolence, tremor, insomnia, hallucinations, and amnesia.
Gastrointestinal:	Constipation, dyspepsia, diarrhea, vomiting, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH.
Dermatologic:	Pruritus, petechiae, urticaria, photosensitivity.
Other:	Polyuria, nocturia.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: erythema multiforme; leukopenia; and extreme elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been limited. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral/LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. Although individual patients may respond to any dosage level, the average optimum dosage range appears to be 180 to 240 mg/day. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

Cardizem 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1771-49). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1772-49). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

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INDERAL* LA brand of propranolol hydrochloride **(Long Acting Capsules)**

DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.

CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum [illegible] concentration when used in the treatment of hypertensive patients

In angina pectoris, propranolol generally redu[illegible] at any given level of effort by blocking the catechola[illegible]te, systolic blood pressure, and the velocity and ext[illegible]anolol may increase oxygen requirements by increasing [illegible]stolic pressure and systolic ejection period The net phys[illegible]-adre[illegible]kade is usually advantageous and is manifested durin[illegible]nd increased work capacity.

In dosages greater than required for beta bloc[illegible], INDERAL also exerts a quinidine[illegible] or anesthetic-like membrane action which affects [illegible]rdiac ac[illegible]otential [illegible] cance of the membrane action in the treatment of [illegible] is [illegible]n

The mechanism of the antimigraine effect of [illegible]as not [illegible]shed. B[illegible] adrenergic receptors have been demonstrated i[illegible]

Beta receptor blockade can be useful in co[illegible]s in w[illegible]tholo[illegible] functional changes, sympathetic activity is detri[illegible] situations in which sympathetic stimulation is vital For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first degree block; 3) bronchial asthma; 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL

WARNINGS. CARDIAC FAILURE Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible)

> IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker In one case this resulted after an initial dose of 5 mg propranolol

PRECAUTIONS. *General:* Propranolol should be used with caution in patients with impaired hepatic or renal function INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant [illegible]-induced [illegible]icity Th[illegible]re no [illegible]-related tumorigenic effects at any of the dosage le[illegible] a[illegible]mals [illegible] not show any impairment of fertility that was attri[illegible]

[illegible]cy: [illegible] Cate[illegible] C. INDERAL has been shown to be embryotoxic in ani[illegible] a[illegible]t 10 [illegible] greater than the maximum recommended human dose. [illegible]ed studies in pregnant women. INDERAL should be used durin[illegible]gnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing M[illegible]rs: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is a[illegible]stered to a nursing woman.

Pe[illegible] Sa[illegible]ven[illegible] in children have not been established.

ADVE[illegible]TIONS [illegible] effects have been mild and transient and have [illegible]rely [illegible]ired [illegible]

C[illegible]vas[illegible]: [illegible]a; [illegible]e; intensification of AV block; hypotension, [illegible], arterial insufficiency, usually of the Raynaud [illegible]e.

Central Nervous System. li[illegible]dedness, mental depression manifested by insomnia, lassitude, weakness, fatigue, r[illegible]le mental depression progressing to catatonia, visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized* The initial oral dose is 80 mg INDERAL LA once daily The usual effective dose range is 160-240 mg once daily The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

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Caution patients about driving, operating hazardous machinery or drinking alcohol during therapy. Limit dose to 15 mg in elderly or debilitated patients. Contraindicated during pregnancy.

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Contraindications: Known hypersensitivity to flurazepam HCl; pregnancy. Benzodiazepines may cause fetal damage when administered during pregnancy. Several studies suggest an increased risk of congenital malformations associated with benzodiazepine use during the first trimester. Warn patients of the potential risks to the fetus should the possibility of becoming pregnant exist while receiving flurazepam. Instruct patient to discontinue drug prior to becoming pregnant. Consider the possibility of pregnancy prior to instituting therapy.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. An additive effect may occur if alcohol is consumed the day following use for nighttime sedation. This potential may exist for several days following discontinuation. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Potential impairment of performance of such activities may occur the day following ingestion. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, abrupt discontinuation should be avoided with gradual tapering of dosage for those patients on medication for a prolonged period of time. Use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in severely depressed patients, or in those with latent depression or suicidal tendencies, or in those with impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins, and alkaline phosphatase; and paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity.

Dosage: Individualize for maximum beneficial effect. *Adults:* 30 mg usual dosage; 15 mg may suffice in some patients. *Elderly or debilitated patients:* 15 mg recommended initially until response is determined.

Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.

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MEETINGS AND LECTURES

The New York State Journal of Medicine *cannot guarantee publication of meetings and lectures unless the information is submitted at least two months prior to the event.*

OCTOBER 1984

AROUND THE STATE

MANHATTAN

Oct 3. **Perspectives on Changing Reimbursements. The New Economics of Medical Care.** 6 Cat 1 credits. *Oct 18–19.* **Adolescent Medicine for the Practitioner.** 14 Cat 1 credits. *Oct 25 & 26.* **A Practitioners Guide to Teenage Health Care.** 12 Cat 1 credits. Warwick Hotel. Info: Ann J. Boehme, CME Coordinator, LIJ-Hillside Medical Center, New Hyde Park, NY 11042. Tel: (212) 470-2114.

Oct 8–10. **Cardiovascular Therapeutics** (co-sponsored with the American College of Physicians). *Oct 27.* **Premenstrual Syndrome—New Findings and Controversies.** 5½ Cat 1 credits. *Oct 29–Nov 2.* **Temporal Bone Surgery.** 45 Cat 1 credits. Mount Sinai Medical Center. Info: Page and William Black Post-Graduate School of Medicine, One Gustave L. Levy Place, New York, NY 10029. Tel: (212) 650-6737.

Oct 10–14. **XV Annual Oculoplastic Surgical Dissection Course.** Waldorf Astoria Hotel. Info: J. Weschner, c/o Dr P. Guibor, 630 Park Ave, New York, NY 10021. Tel: (212) 734-1010.

Oct 11. **Geriatric Medical Education Imperative.** Academy of Medicine. Info: Office of Medical Education, The New York Academy of Medicine, 2 East 103rd St, New York, NY 10029. Tel: (212) 876-8200.

Oct 16. **How to Develop a Research Project.** *Oct 24.* **From Conception to Concept: Risk Factors for Communication Development.** *Oct 26.* **Cosmetology Symposium.** Beth Israel Medical Center. Info: Post-Graduate Medical Education Office, Beth Israel Medical Center, 10 Nathan D. Perlman Place, New York, NY 10029. Tel: (212) 420-2849.

Oct 15–19. **Renal Biopsy in Medical Diseases of the Kidneys.** 35 Cat 1 credits. *Dec 6 & 7.* **Current Topics in Gastroenterology—1984.** 13½ Cat 1 credits. College of Physicians & Surgeons of Columbia University. Info: Dr Elizabeth C. Gerst, Director, Continuing Education Center, 630 West 168th St, New York, NY 10032. Tel: (212) 694-3682.

Oct 18–20. **An Eclectic Retrospective: Updated Selections from a Decade of Dermatopathology Symposia.** 19 Cat 1 credits. NYU School of Medicine. Info: Registration Office, NYU Post-Graduate Medical School, 550 First Ave, New York, NY 10016. Tel: (212) 340-5295.

Oct 24. **Aging and the Dementias.** 6 Cat 1 credits. *Oct 25.* **Aging in the 21st Century.** 6 Cat 1 credits. Rockefeller University. Info: The Montefiore Centennial Series, Montefiore Medical Center, 111 East 210th St, The Bronx, NY 10467. Tel: (212) 920-4011.

Oct 24–26. **Selected Topics in Allergy & Immunology.** 20 Cat 1 credits. Columbia College of Physicians & Surgeons, New York City. Info: Dr Elizabeth C. Gerst, CME, College of Physicians & Surgeons, 630 W. 168th St, New York, NY 10032. Tel: (212) 694-3682.

Oct 26–27. **Reproductive Endocrinology and Infertility.** 14 Cat 1 credits. Lenox Hill Hospital. Info: Lauren H. Straub, Lenox Hill Hospital, 100 E 77th St, New York, NY 10021. Tel: (212) 794-4500.

Oct 27. **Premenstrual Syndrome: New Findings and Controversies.** 5½ Cat 1 credits. Info: Mount Sinai Medical Center, Page & William Black Post-Graduate School, One Gustave L. Levy Place, New York, NY 10029. Tel: (212) 650-6737.

Dec 6 & 7. **Current Topics in Gastroenterology—1984.** 13½ Cat 1 credits. Columbia University. Info: Dr Elizabeth C. Gerst, Continuing Education Center, 630 W 168th Street, New York, NY 10032. Tel: (212) 694-3682.

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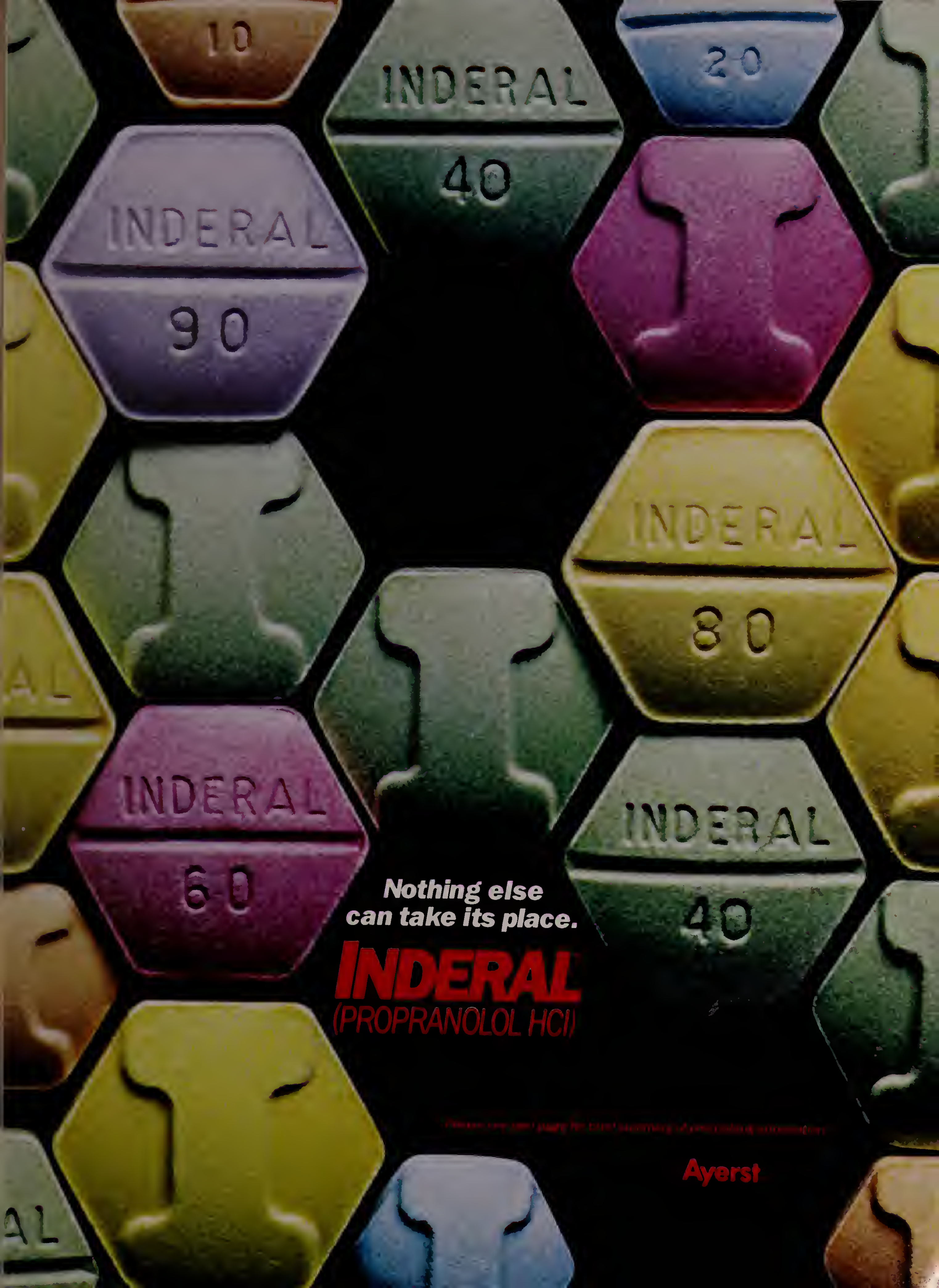
Oct 4. **Therapy of Rheumatoid Arthritis.** 2 Cat 1 credits. *Oct 11.* **Drugs and the**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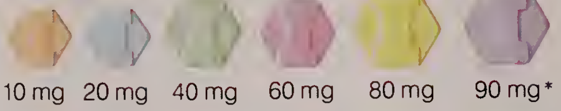

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR)

INDERAL® (propranolol hydrochloride) Tablets

CLINICAL PHARMACOLOGY

The Beta-Blocker Heart Attack Trial (BHAT) was a National Heart, Lung and Blood Institute-sponsored multicenter, randomized, double-blind placebo-controlled trial conducted in 31 U S centers (plus one in Canada) in 3,837 persons without history of severe congestive heart failure or presence of recent heart failure, certain conduction defects, angina since infarction, who had survived the acute phase of myocardial infarction Propranolol was administered at either 60 or 80 mg t i d based on blood levels achieved during an initial trial of 40 mg t i d Therapy with INDERAL, begun 5-21 days following infarction, was shown to reduce overall mortality up to 39 months the longest period of follow-up This was primarily attributable to a reduction in cardiovascular mortality The protective effect of INDERAL was consistent regardless of age, sex or site of infarction Compared to placebo, total mortality was reduced 39% at 12 months and 26% over an average follow-up period of 25 months The Norwegian Multicenter Trial in which propranolol was administered at 40 mg q i d gave overall results which support the findings in the BHAT

Although the clinical trials used either t i d or q i d dosing, clinical, pharmacologic and pharmacokinetic data provide a reasonable basis for concluding that b i d dosing with propranolol should be adequate in the treatment of post-infarction patients

CLINICAL In the BHAT, patients on INDERAL were prescribed either 180 mg/day (82% of patients) or 240 mg/day (18% of patients) Patients were instructed to take the medication 3 times a day at mealtimes This dosing schedule would result in an overnight dosing interval of 12 to 14 hours which is similar to the dosing interval for a b.i.d regimen In addition, blood samples were drawn at various times and analyzed for propranolol When the patients were grouped into tertiles based on the blood levels observed and the mortality in the upper and lower tertiles were compared, there was no evidence that blood levels affected mortality

PHARMACOLOGIC Studies in normal volunteers have shown that a 90 mg b i d regimen maintains beta blockade at, or above, the minimum for 60 mg t i d dosing for 24 hours even though differences occurred at two time intervals At 10-12 hours after the first dose of the day, t i d dosing gave more beta blockade than b i d dosing, at 20-24 hours the trend of the relationship was reversed These relationships were similar in direction to those observed for plasma propranolol levels (see Pharmacokinetics)

PHARMACOKINETIC A bioavailability study in normal volunteers showed that the blood levels produced by 180 mg/day given b i d are below those provided by the same daily dosage given t i d at 10-12 hours after the first dose of the day but above those of a t i d regimen at 20-24 hours However the blood levels produced by b i d dosing were always equivalent to or above the minimum for t i d dosing throughout the 24 hours In addition, the mean AUC on the fourth day for the b i d regimen was about 17% greater than for the t i d regimen (1,194 vs 1,024 ng/ml• hr)

CONTRAINDICATIONS

INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL

WARNINGS

CARDIAC FAILURE Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure Although beta blockers should be avoided in overt congestive heart failure if necessary they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can in some cases, lead to cardiac failure Therefore at the first sign or symptom of heart failure the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible)

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and in some cases, myocardial infarction following abrupt discontinuance of INDERAL therapy Therefore when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks and the patient should be cautioned against interruption or cessation of therapy without the physician's advice If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris Since coronary artery disease may be unrecognized it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) – PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS INDERAL (propranolol hydrochloride) should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors

MAJOR SURGERY The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures

INDERAL, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e g , dobutamine or isoproterenol However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers

DIABETES AND HYPOGLYCEMIA Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin

THYROTOXICOSIS Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker In one case this resulted after an initial dose of 5 mg propranolol

PRECAUTIONS

General Propranolol should be used with caution in patients with impaired hepatic or renal function INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure Patients should be told that INDERAL may interfere with the glaucoma screening test Withdrawal may lead to a return of increased intraocular pressure

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DRUG INTERACTIONS Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity There were no drug-related tumorigenic effects at any of the dosage levels Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug

Pregnancy Pregnancy Category C INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose

There are no adequate and well-controlled studies in pregnant women INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Nursing Mothers INDERAL is excreted in human milk Caution should be exercised when INDERAL is administered to a nursing woman

Pediatric Use Safety and effectiveness in children have not been established

ADVERSE REACTIONS

Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy

Cardiovascular bradycardia, congestive heart failure, intensification of AV block hypotension, paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type

Central Nervous System Lightheadedness, mental depression manifested by insomnia, lassitude weakness, fatigue, reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics

Gastrointestinal nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis

Allergic pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory bronchospasm

Hematologic agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Auto-Immune In extremely rare instances, systemic lupus erythematosus has been reported

Miscellaneous alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol

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NEW YORK STATE
JOURNAL OF MEDICINE

September 1984 • Volume 84, Number 9

COMMENTARIES

Infection and bone marrow transplantation

The increasing use of human bone marrow transplantation for acute leukemia, aplastic anemia and various immune deficiency disorders,[1,2] has been associated with a variety of opportunistic infections.[3,4] This was predictable, since both the underlying disease and the therapeutic measures employed to permit donor marrow proliferation are often associated with marked host immunosuppression.[5–7] Indeed a significant number of patients with the above disorders develops infections, most often bacterial, before undergoing transplantation.[7]

Fungal infections appear to have an earlier onset than bacterial infections in bone marrow transplant recipients.[6,7] Although this might seem surprising, one must recall that prior to transplantation these patients are often treated with combinations of antimetabolites, alkalating agents, corticosteroids, radiation and broad spectrum antibiotics.[7] The bone marrow recipient is then subjected to further immunosuppressive therapy which results in abnormal humoral and cell mediated immunity, often lasting for months.[8] A profound granulocytopenia is also frequently present.[7] This bacteriologically sterile, immunosuppressed setting is ideal for colonization and ultimately infection by opportunistic fungi. Indeed most of these agents are ubiquitous and many represent normal flora.

Fungal infections in immunocompromised patients appear to be increasing in frequency in recent years.[9] Although *Candida albicans* is still the major culprit, *Candida tropicalis* has also emerged as a major pathogen.[9] Other important mycotic infections include aspergillosis, cryptococcosis and mucormycosis. In this issue of the *Journal*, El-Ani and Castillo[10] report on a patient with a myeloproliferative disorder who received a T-cell depleted marrow transplant from his father. The patient subsequently died with disseminated infection caused by *Trichosporon beigelii*. This species and *Trichosporon capitatum* are recognized as pathogens in the immunocompromised host.[11] A recent study of 353 patients undergoing allogeneic bone marrow transplantation or chemotherapy for hematologic malignancies demonstrated this species in the stool, urine or respiratory specimens in 13 (3.7%) individuals.[11] The emergence of members of this species as opportunistic pathogens is probably related to prior emperic therapy with both oral nonabsorbable antibiotics and amphotericin B. Trichosporon species do not appear to be as sensitive to amphotericin B as are many other fungi, and this might favor selective colonization and subsequent invasion of the host by this fungus.

The diagnosis of most deep-seated fungal infections is often problematic; pneumonia might not be accompanied by purulent sputum, and severe dyspnea might be the only clinical finding. A gradual and progressive decrease in urine output might be the only indication of fungal involvement of the kidneys. Blood cultures are frequently negative. In addition, the reduced inflammatory process often masks symptoms associated with septic thrombosed blood vessels in certain organ systems. Daily complete physical evaluations and frequent culturing of the blood, urine, sputum and stool for fungi are therefore essential.[11] New findings should never go unattended. Vague headaches might be the only indication of fungal meningitis.

Finally, some comment should be made about interstitial pneumonitis in allogeneic marrow transplantation patients. Various agents, primarily viral (cytomegalovirus, herpes zoster, herpes simplex) and protozoal (*Pneumocystis car-*

inii, toxoplasma) have been implicated.[7,12] Of these, cytomegalovirus (CMV) is thought to be the most common agent,[13,14] and the CMV serologic status of patients at the time of transplant appears to be important in the pathogenesis of this lung disorder.[15] Patients who are seropositive at the time of transplantation have a higher incidence of generalized CMV infection than seronegative patients. Transfusion with seropositive or seronegative granulocytes does not appear to increase the incidence of CMV infection in this group. Seronegative patients (before transplantation) who do not receive granulocytes probably acquire CMV infection as a result of platelet or erythrocyte transfusions, or both. Seronegative patients who are recipients of seropositive granulocytes appear to have a significantly greater risk of CMV interstitial pneumonitis.[15]

These observations are of great importance, since CMV interstitial pneumonitis is a major cause of death in allogeneic marrow transplant patients.[13,14] In addition, preliminary evidence suggests that CMV infection, whether primary or secondary, might also be a major cause of T-cell alterations in these patients. The high suppressor T-cell activity and the impaired helper T-cell activity associated with CMV infection could result in an increased frequency of opportunistic infections.[15]

There seems to be a cycle forming: treatment of the underlying disease may predispose a patient to opportunistic infections, usually bacterial; therapeutic preparation for bone marrow transplantation appears to cause early onset of fungal infections; and CMV infection in the transplant recipient often results in interstitial pneumonitis and other opportunistic infections. None of these observations diminishes the value of bone marrow transplantation in certain disease states. They do, however, point to the need for long-term studies that examine the possible influence of a large number of therapeutic variables on the type and frequency of opportunistic infections in this setting.

NICHOLAS J. VIANNA, MD
Director
Division of Health Risk Control
New York State Health Department
Albany, NY 12237

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Aspergillosis infection following radiotherapy

The case reports published by Cancroft et al[1] in this issue of the *Journal* stress the importance of the changing spectrum of aspergillosis. Previous reports have focused on the underlying and exacerbating factors that enable *Aspergillus* to proliferate. The cases discussed in this issue illustrate the benign mycetoma, one of at least four clinical syndromes associated with aspergillosis, or an aspergilloma, occurring in an area of the lung that was previously irradiated.

The "benign fungus ball" occurs as a saprophytic growth within an area of lung parenchyma damaged by tuberculosis, sarcoidosis, saccular bronchiectasis, bullae, pulmonary infarctions, necrotic neoplasms, lung cysts, areas of previous lung resection, and histoplasmosis cavities.[2–4] Recently, the prevalence of tuberculosis has decreased and is no longer the major predisposing condition to aspergillosis.[5] Several reports, including this one, suggest that the fibrosis caused by previous radiotherapy may serve as a site for colonization by *Aspergillus*,[2,5–7] and they stress the importance of early recognition and identification of this mycetoma. *Aspergillus fumigatus* and *Aspergillus flavus* account for the majority of these infections.[8]

Several factors need to be considered prior to attributing a cause and effect relationship between radiotherapy and subsequent aspergilloma development in patients with neoplastic diseases. A patient receiving radiotherapy to the chest for lung cancer may also have chronic obstructive pulmonary disease, a history of tuberculosis, or bronchiectasis. In addition, effective radiation therapy may cause tumor necrosis which could predispose the patient to subsequent mycetoma development. The first case described by the authors may represent one example.

The aspergilloma can subsequently follow several clinical courses depending on the host response. The cases described by Cancroft et al followed the course of a "benign fungus ball." This "benign" syndrome has the characteristic finding of a crescent sign on chest film and radiologic evidence of cavitation by chest tomography or a computed tomography scan of the chest, which are suggestive of but not pathognomonic for an aspergilloma. The benign mycetoma follows a chronic course, and no evidence of invasiveness or dissemination should be apparent. The diagnosis is dependent upon the radiographic findings, serum precipitating antibodies to aspergillus antigens, and a positive culture result for *Aspergillus* if tissue is obtained. Sputum cultures lack sensitivity and specificity and cannot be relied on to confirm the diagnosis.[3] The mycetoma may progress or may undergo spontaneous lysis, as occurs in 10% of the cases.[9] It can also remain stable for many years or develop exacerbations of hemoptysis. The latter occurs in more than half the patients with this disorder, and a fourth of these patients may go on to develop life threatening hemorrhage.[8,10] Patients with recurrent severe hemoptysis should be considered for surgery, but routine surgical resection of an aspergilloma is not recommended.[3]

A chronic necrotizing pulmonary aspergillosis may also occur in patients with mycetomas that develop in radiation-induced fibrotic areas of the lung. This syndrome follows an indolent cavitary process but can be distinguished from the "benign" mycetoma by the presence of systemic symptoms, such as fever, cough, and weight loss, and pulmonary infiltration by *Aspergillus*. The clinical criteria for defining this syndrome have been reviewed by Binder et al[2] and include a positive culture for *Aspergillus* from bronchoscopy, percutaneous aspiration, lung biopsy, or sputum along with a clinical response to antifungal therapy, exclusion of other fungi or bacteria, absence of disseminated *Aspergillus*, chronicity, and exclusion of severe immunosuppression. These patients often respond to amphotericin B, with or without 5-fluorocytosine, as well as surgery for selected cases. Although these patients were not significantly immunosuppressed, 'mild immunosuppression' secondary to debilitation, alcoholism, sarcoidosis, diabetes mellitus, connective tissue disorders, chronic obstructive pulmonary disease, or low dose steroid therapy was apparent in most patients.[2,7]

The invasive form of aspergillosis may complicate a mycetoma but often occurs in the absence of a previous aspergilloma.[11-14] The majority of such cases involved hematologic malignancies, and the patients were treated with aggressive chemotherapy. Disseminated aspergillosis may extend from the lung to involve the intestines, brain, kidneys, liver, and esophagus as well as other organs. The overall prognosis for this disorder is poor, and, as in the chronic necrotizing form of aspergillosis, the disorder responds best to early therapy with antifungal medication and treatment of the underlying problem in the host. Several diagnostic tests have proven useful in detecting invasive aspergillosis. A new radioimmunoassay for *Aspergillus fumigatus* antigen appears to be a highly specific and moderately sensitive test for this invasive form.[15]

Finally, the mycetoma may be associated with an allergic bronchopulmonary aspergillosis. Patients may demonstrate wheezing associated with pulmonary infiltrates, eosinophils in both blood and urine, elevated levels of immunoglobulin (Ig) E, and serum precipitating antibodies to aspergillus antigens. This syndrome usually responds to steroids.[16] In addition to this type I allergic reaction, a type III Arthus-like reaction may occur.

Thus, the clinical spectrum of aspergillosis in the patient with cancer can take many forms depending on various predisposing factors and the host response. The mycetoma may maintain a relatively benign course as illustrated in the reports by Cancroft et al, but it may also develop into one of the other, more aggressive syndromes associated with aspergillosis. These must be considered, since an aspergilloma can be a complication of cancer therapy, and *Aspergillus* is the second most common fungal infection in patients with cancer.

PAUL P. CARBONE, MD
JOHANNES C. NUNNINK, MD
Department of Human Oncology
Wisconsin Clinical Cancer Center
University of Wisconsin
600 Highland Avenue
Madison, WI 53792

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The changing pathogenesis of aspergilloma or "fungus ball"

The fungal ball is regarded as a saprophytic manifestation of *Aspergillus* growing in a preformed and poorly drained lung space. Mycetomal disease rarely has been described with other fungi including *Coccidioides immitis*, *Mucor*, *Penicillium* species and *Petriellidium boydii*, but the majority of such cases remain controversial. The occurrence of aspergilloma in the general population is unknown, but has been estimated to be 0.01% to 0.02%.

Most aspergillomas develop in the wake of a pulmonary insult that results in the formation of a lung cavity. Historically, the most common antecedent disease is tuberculosis. Patients with tuberculous cavities have been reported to have an 11% to 17% incidence of aspergilloma.[1] Other conditions associated with development of aspergilloma include sarcoidosis, cavitary neoplasm, pulmonary fibrosis, lung abscess, bronchial cyst, asbestosis, histoplasmosis, blastomycosis, ankylosing spondylitis, bronchiectasis, pneumonia, cyanotic heart disease, pulmonary infarction, allergic bronchopulmonary aspergillosis and invasive aspergillosis.[2,3]

In this issue of the *Journal*, Cancroft et al[4] report two patients with malignant tumors who developed aspergilloma in post-radiation cavities. This represents part of a clinical setting that is rapidly evolving as one of the major disorders associated with development of pulmonary aspergillosis and, in particular, aspergilloma. Aspergillosis is the second most frequent fungal infection encountered in immunocompromised patients.[5] In such patients, *Aspergillus* frequently causes a necrotizing pulmonary vasculitis with resultant hemorrhagic infarction. When invasive disease is severe, it may also result in cavity formation with development of acute aspergilloma[6-10] or a subacute indolent process resembling chronic cavitary tuberculosis.[11,12] In some cases of "fungal balls" complicating invasive pulmonary aspergillosis, the lesion may really be "lung balls," with necrotic pulmonary tissue filling the cavity, rather than fungal hyphae.[13]

Development of single or multiple pulmonary aspergilloma is not an uncommon occurrence in acute lymphocytic or myelogenous leukemia, lymphoma, or granulocytopenia from any cause.[2,5] Antineoplastic agents and cytotoxic drugs act as predisposing factors by inducing leukopenia, immunosuppression, and perhaps by enhancing gastrointestinal portals of entry by direct tissue toxicity.[5] The lesions are formed by colonization of necrotic lung tissue resulting from concomitant bacterial infection, pulmonary embolic phenomena and quiescent preexisting cavitary or cystic lung disease. When multiple aspergillomas are noted, the most likely pathogenetic mechanism is direct hematogenous spread.[2] The radiographic appearance may be that of an air crescent surrounding a dense opacity (Monad's sign) classically associated with aspergilloma in patients with preexisting lung disease.[2]

A subacute, suppurative process may initiate a chronic, invasive form of aspergilloma. Patients are usually middle-aged with evidence of impairment of host defenses such as those having a history of a solid tumor, diabetes mellitus, a rheumatic disorder, poor nutrition, or corticosteroid therapy. The fungal ball may develop in an indolent, necrotizing fashion or may later become acute with occasional evolution into a fulminating disease with a fatal outcome.[11,12] The term "chronic necrotizing pulmonary aspergillosis" has been employed to define this as a discrete clinical entity,[11] but its validity is questionable. Since the first case of aspergilloma in a cancerous cavity was described by Mays and Hawkins,[14] many similar observations have been made.[2,3,11,15] Cancroft et al[4] report two cases of mycetoma in post-radiation pulmonary cavities, one of which had a typical air crescent. These cases are unique, since previous reports have cited post-radiation fibrosis as the major underlying lung condition.[11,16,17] As we become more successful in treating all forms of neoplasms, I predict the incidence of aspergilloma in the immunocompromised patient will increase significantly.

Earlier diagnosis and improved chemotherapy of mycobacterial disease have resulted in a decrease of aspergilloma as a common sequelae of tuberculosis. On the other hand, improved survival rates for malignancies have resulted in an increased frequency of mycetoma as a manifestation of acute or chronic invasive aspergillosis. The clinician should be aware of this possibility, since the outlook favors continuation of this shift in pathogenesis.

EMIL J. BARDANA, Jr, MD
Professor of Medicine
Head of the Allergy Section
Oregon Health Sciences University
Portland, OR 97201

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Lead poisoning: a historical overview

The article in this issue of the *Journal* on occupational lead exposure by Fischbein et al[1] serves as a reminder that one of the oldest preventable diseases known to man is still with us. Outbreaks of lead poisoning have occurred since antiquity. The Greek poet-physician Nicander described the disease over 2,000 years ago. Roman food and drink, particularly reinforced wines, were heavily contaminated with lead. And, Sara C. Bisel, PhD, a classical archaeologist and physical anthropologist, reported in May 1983 at the annual meeting of the American Association for the Advancement of Science that chemical analysis of skeletons of Romans, killed by the eruption of Mount Vesuvius in 79 AD, indicated high lead content in at least eight individuals.

The Massachusetts Bay Colony forbade rum distillation in leaded stills in 1723 to prevent "dry gripes," an intestinal condition. In 1767 Sir George Baker blamed "the endemic colic of Devonshire" on the use of lead-lined troughs in the making of apple cider.[2] The dangers of occupational exposure to lead have been well documented for over a century, and since the early 1930s there has been increasing study and resulting concern about the problem of childhood lead poisoning associated with the ingestion of leaded paint. This led to the banning of leaded paint for interior use in the 1950s. Why then is lead poisoning, a truly preventable disease, still a cause for concern and the subject of so much study and worldwide controversy in the 1980s?

To understand the answer to this question, one must know the history of the fight against lead poisoning—one of the outstanding success stories in public health. Unfortunately, the failure to eradicate the disease also reveals the enormous frustrations and disappointments of workers in the field of public health. The intense battle against childhood lead poisoning illustrates the problem.

In the 1950s and 1960s, pediatricians, public health professionals, and other concerned citizens were appalled by the increasing number of inner city children living in substandard housing who were suffering from severe consequences of lead intoxication, including permanent brain damage and death. A national outcry resulted in the federal government appropriating millions of dollars to fight the "silent enemy." By the early 1970s, most of the major cities had begun federally funded childhood lead poisoning control programs. The conquest of childhood lead poisoning seemed within reach. Children were screened, treated, monitored, and removed from environments with high levels of lead. Data were collected and analyzed by the Centers for Disease Control, and a uniform reporting system was developed. As the number of children with extremely high blood lead levels dropped, as a result of aggressive control programs, reports began to come in from around the country of children with elevated lead levels not associated with exposure to lead paint.

Investigators searched for other sources of lead. Baby food, canned milk, and other canned foods were found to contain unacceptable concentrations of lead as a result of contamination from lead solder during the canning process. Bottles of fruit juices, particularly apple juice, were detected that had been contaminated by lead arsenate used as a pesticide spray on the growing fruit.

As each new source of lead was revealed, steps were taken to eliminate or mitigate the exposure. In 1970, in New York City, over 87,000 blood tests were performed on children; 2,700 results over 55 mg/dL were reported. By 1974, only 500 out of 125,000 tests were reported over 55 mg/dL. But now evidence was piling up that lower levels of blood lead were associated with subtle but serious neurobehavioral changes, and that many children were still being damaged. Allowable blood lead levels were lowered from 60 mg/dL to 40 mg/dL. Laws were proposed that further limited the concentration of lead in interior paint.

At this point, the Lead Industries Association, Inc (a nonprofit trade association whose member companies include most domestic producers and commercial consumers of lead) and some paint manufacturers fought the changes citing severe economic consequences to the industry and lack of demonstrable need. Testimony was presented to congressional subcommittees. The evidence supplied by the public health community was overwhelming and the laws were changed.

Research continued, and the association of blood lead levels to the amount of lead released into the atmosphere was probed. The records of 170,000 children screened by the New York City Lead Poisoning Control Program during 1970–1976 were reviewed, and venous blood lead levels and demographic data were analyzed.[3] The geometric mean of the blood lead levels showed a consistent cyclical variation superimposed on an overall decreasing trend with time for all ages and ethnic groups studied. Regression analysis indicated a significant statistical correlation between the geometric mean blood lead level and the ambient air lead level, after adjustments were made for age and ethnic group. As a result of this study and others, the Environmental Protection Agency (EPA) proposed a standard for the allowable concentration of lead in ambient air. Again the lead industry, including such giants as E I du Pont de Nemours & Co and the International Lead-Zinc Research Organization (ILZRO), opposed the standard; they were joined by the American Petroleum Association (an oil industry trade association), gasoline being the major source of air lead. Economics and the lack of demonstrable need were cited. Testimony was provided to the EPA and to Congress.

Again the public health community prevailed, and more stringent standards were set.

Continuing clinical research revealed that children were being damaged by levels once thought acceptable,[4] and the allowable blood levels were lowered from 40 mg/dL to 30 mg/dL. Studies showed a clear association between the amount of lead in gasoline sold in an area and the blood lead levels of children screened.[5] Data from the second National Health and Nutrition Examination Survey appeared to show a strong correlation between declining blood lead levels and the reduction in the amount of leaded gasoline sold. Further reductions in air lead were proposed, and the phase down and eventual banning of lead in gasoline was recommended. Again the lead industry, led by ILZRO, the Ethyl Corporation (the nation's leading producer of lead additives for gasoline) and others, fought back. Experts were flown in from around the world to testify before scientific committees of the EPA. Again the public health community rallied. William D. Ruckelshaus, administrator of the EPA, announced at a news conference on July 30, 1984, that the agency's intention was total elimination of leaded gasoline by 1995. Citing "overwhelming" evidence that lead in gasoline is a serious threat to health, Mr Ruckelshaus stated that the "social and economic benefits will be very substantial, and the costs will be minimal."

Over the years, the seemingly endless resources available to industry to fund research and to hire experts to challenge the scientific validity of the various studies that document the adverse health effects of lead have been a constant source of envy and frustration to the public health community, who must live within the contraints of very limited funding. It is also a severe disappointment to witness the defection of former colleagues, who were wooed by the availability of industry support for their research.

One of my professors of health administration, Dr Lowell E. Bellin, once told me that "Public health is incrementalism"; everything is accomplished one slow step at a time. And Dr John J. Hanlon writes that public health is applied social science.[6] I would add that it is also the integration of scientific fact with political and economic realism. And that is why, in the 1980s, lead poisoning, a truly preventable disease, is still with us, and why Dr Fischbein et al remind physicians to consider it in the differential diagnosis when treating individuals in certain occupational groups such as shipbuilders, construction crews, bridge maintenance workers, burners and welders, and others. Whereas decreasing blood lead levels in the general population, particularly in inner city children represent one of the outstanding success stories of public health, the struggle to reduce environmental and occupational exposure to lead points out the frustrations and disappointments with which the public health community must contend.

ANITA S. CURRAN, MD
Commissioner
Westchester County
Department of Health
112 East Post Road
White Plains, NY 10601

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NMR: a new perspective on medicine

For nearly four decades the nuclear magnetic resonance (NMR) phenomenon has provided physicists and chemists with an invaluable window to the structure, motion, and identity of molecules and their environments. Now NMR technology has advanced on medicine, providing high-resolution anatomical images that can identify pathologic changes, as well as profiles of metabolite concentrations that directly reflect the state of health of tissue in vivo.

The power of NMR technology lies in its versatility.[1] Since NMR occurs in any nucleus with an odd number of either protons or neutrons, many naturally occurring, non-radioactive isotopes such as hydrogen (^{1}H), carbon (^{13}C), phosphorus (^{31}P) and sodium (^{23}Na) are accessible to NMR examination. Such nuclei are slightly magnetic and therefore weakly polarize when placed in an external magnetic field. ^{1}H provides the greatest signal-to-noise ratio, constitutes two thirds of the nuclei in the body, and is therefore the most popular for imaging. ^{31}P and ^{13}C resonances are orders of magnitude less intense but nevertheless provide valuable metabolic information.

Three types of magnetic field are necessary for NMR imaging: a strong static magnetic field for polarizing the nuclei; a tuned radio frequency field for exciting the resonances; and x-, y-, and z- magnetic field gradients for spatially encoding the NMR signal.[1] The different nuclear resonances are selected by precisely matching the frequency of the exciting field to the desired nuclear resonance within the strong static field. For example, in a static magnetic

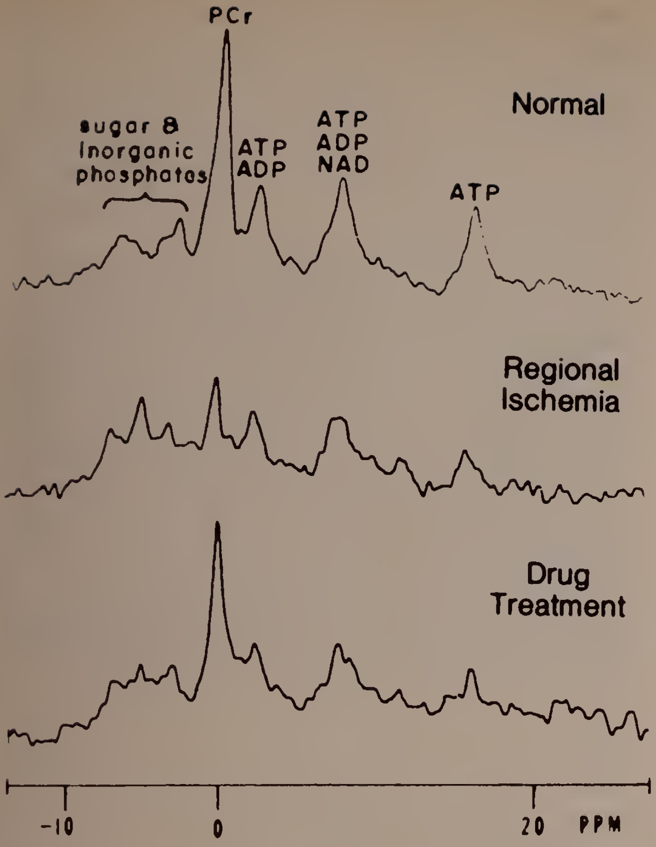

FIGURE 1. Localized ^{31}P NMR spectrum from a rabbit heart showing the effect of regional ischemia induced by ligating the left anterior descending coronary artery, and its response to drug treatment.[3] The regionally ischemic spectrum shows depletion of the phosphocreatine (PCr) reservoir, and an increase in inorganic phosphates. A normal appearing spectrum is observed with subsequent drug treatment with verapamil and the ligature still in place. The horizontal axis is the NMR frequency expressed in parts per million relative to the phosphocreatine resonance. (ATP = adenosine triphosphate.)

field of 1.5 Tesla (T) (A tesla is a unit of magnetic flux density equal to one weber per square meter.), ^{1}H resonates at about 63.8655 MHz, ^{31}P at about 25.8525 MHz, and ^{13}C at about 16.0575 MHz. These frequencies lie in the radio frequency realm of the electromagnetic spectrum. Consequently NMR signals are detected with sensitive radio receivers.

Once excited, the NMR signal decays back to equilibrium with characteristic time constants that depend on the molecular-level motion in the neighborhood of the resonant nuclei. Since physiological and disease processes also occur at the molecular level, these time constants—termed T_1 and T_2 relaxation times—vary dramatically among normal and pathologic tissues and constitute the principal source of contrast in NMR images.[1] Other parameters such as blood flow velocity[2] and diffusion are also accessible to NMR analysis.

Chemical information is manifested in the NMR signal as minute variations of the NMR frequencies of nuclei located at different sites on a molecule owing to different electron distributions. The spectrum of NMR frequencies of each molecule is a characteristic "fingerprint" that can be used for identification. For example, in vivo ^{31}P spectra contain resonances corresponding to the metabolites phosphocreatine (PCr), adenosine triphosphate (ATP), sugar phosphate (SP), and inorganic phosphate (Pi). ATP provides fuel for muscular contraction, PCr is a "reservoir" for cellular energy and Pi is an end product which increases rapidly with the onset of ischemia. Figure 1 shows ^{31}P rabbit heart spectra as a function of ischemia and drug treatment with verapamil.[3] Highly uniform static magnetic field strengths, typically in excess of 1 T, are necessary to resolve chemical spectra.[4] We recently obtained ^{1}H, ^{31}P, and ^{13}C spectra from the head and limbs using a 1.5 T system.[4–6]

Strong magnetic field strengths have the added advantage of improved image signal-to-noise ratios, reflecting the ability of stronger fields to polarize more nuclei which are

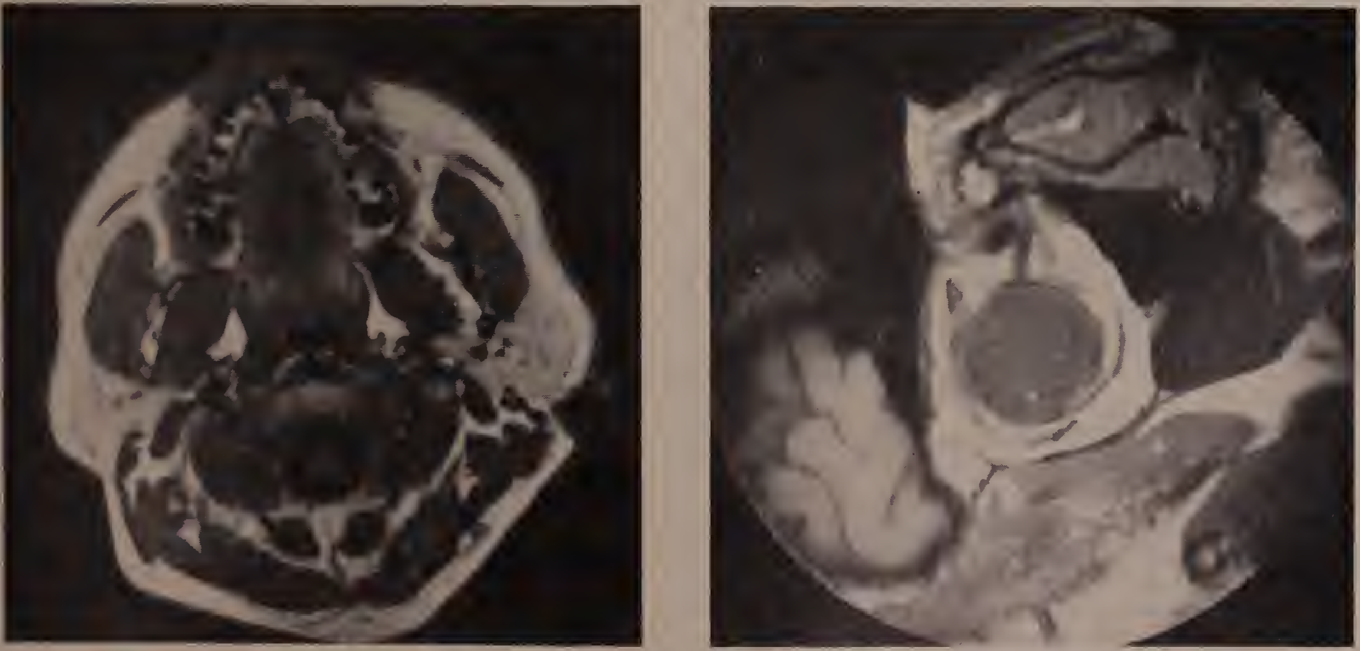

FIGURE 2. Left, transverse ^{1}H NMR image through the nose recorded in 102 s at 1.5 T.[4] The image consists of 256 × 256, 1 mm × 1 mm × 4 mm points. Right, coronal ^{1}H NMR image through the eye with 0.5 mm × 0.5 mm × 4 mm resolution recorded with a surface coil at 1.5 T.

otherwise disrupted by thermal motion. Traditionally, the signal-to-noise ratio improves as seven fourths the power of the field,[7] but this probably reduces to linear dependence with large samples such as the body.[4,8] Improved signal-to-noise ratios can be translated into better image quality, finer spatial resolution, or reduced scan times when signal averaging is otherwise involved. Examples of a ^{1}H image of the head and a high resolution ^{1}H image of the eye recorded at 1.5 T are shown in Figure 2.[4]

Contrast in NMR images and chemical spectra can be enhanced by introducing contrast agents, similar to those used with computed tomography. In NMR the agents are simple paramagnetic compounds containing ions such as iron (Fe^{+++}), manganese (Mn^{++}), or gadolinium (Gd^{+++}) in organic chelates. Such substances, which have been termed magnetopharmaceuticals,[1] alter image contrast in accessible regions by substantially changing the local NMR relaxation times. Edge enhancement of cerebral tumors[9] exemplifies this application.

With such a plethora of motional, chemical, and contrast parameters and probes available to explore each of the many magnetically resonant nuclei present in the body, a sparkling future for NMR technology in diagnostic medicine seems assured. The technique employs no ionizing radiation and indeed has minimal associated hazards.[10]

PAUL A. BOTTOMLEY, PhD
General Electric Corporate Research
and Development Center
PO Box 8
Schenectady, NY 12301

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AIDS: neither new nor transmissible?

It is the position of the Centers for Disease Control that the viral agent that causes the acquired immunodeficiency syndrome (AIDS) has been identified, although investigators continue to puzzle over the nearly equal incidence of AIDS in males and females in Zaire in contrast to the overwhelmingly male incidence in the United States.[1] Since I am unaware of any other example of such variability of sexual preference by an infecting organism in different parts of the world, I remain skeptical that AIDS is caused by a transmissible agent. Rather, it is the result of an immunologic paradox in which hyperfunction of humoral immunity results in hypofunction of cellular immunity.

It is possible that its counterpart, or more accurately its prototype, has always been present among the inhabitants of countries with poor sanitation, especially those in the tropics. The appearance of AIDS in the United States correlates with the emergence of homosexuals from clandestine relationships to open expression of their sexual preferences. A result of this recent openness is that it is now commonplace for a homosexual to have sexual relationships, including rectal intercourse, fellatio after rectal intercourse and oral-anal contact with more than a thousand different partners. This exposure to many different enteric microorganisms can create in homosexual communities within a highly developed nation, a situation similar to that found in nations where primitive sanitary facilities result in endemic infections with enteric organisms because of ingestion of contaminated food and water. The immunogenicity of these organisms, including bacteria—even the common coliforms—protozoan parasites and viruses is well established in the human being. The presence of large numbers of antibodies to these organisms, especially the bacteria, should be expected in promiscuous homosexuals as well as in inhabitants of countries with poor sanitation.

If this analogy of life styles is accurate, the current theory that AIDS is a new and transmissible disease may be incorrect. It is possible to use available knowledge of the immune system to explain the immunologic abnormalities found in patients with AIDS and to suggest that similar abnormalities may also be found in non-homosexual inhabitants of such countries as Haiti and the nations of equatorial Africa.

Early studies of the immune system involved learning how it is stimulated to produce useful defense mechanisms. More recent work has focused on learning how the immune system is restrained. These studies have confirmed the network theory, which holds that antibodies and immune cells produced in response to antigenic stimulation are themselves antigenic to the host and can provoke a suppressor response, called the anti-idiotype response, which will ultimately limit their production.[2]

Two frequently reported immunologic abnormalities in homosexuals with AIDS are increased levels of suppressor T lymphocytes and increased numbers of antigen-antibody complexes.[3] Studies have shown that antigen-antibody complexes are much more efficient in stimulating the proliferation of suppressor T lymphocytes against antibody production—idiotype-specific suppressor T cells—than are antibodies alone.[4] Therefore, promiscuous homosexuals or inhabitants of countries with poor sanitation, who are repeatedly bombarded by a myriad of antigens from enteric microorganisms may be expected to generate large concentrations of idiotype-specific suppressor T cells directed to the control of the immune responses induced by these many antigens. Intravenous drug abusers and patients with hemophilia who are treated with factor VIII concentrates are also exposed to a multitude of antigens and might be expected to have similar immune responses.

Defective cellular immune function may also be explained by the presence of excessive numbers of antigen-antibody complexes. There are three types of mononuclear cells that serve to provide cellular immunity against specific target cells: macrophages; killer lymphocytes which react by means of antigen-dependent cellular cytotoxicity; and the cytotoxic T lymphocytes. The common finding among these three cell types is the presence of specialized binding sites for antibodies, the Fc receptors.[5] When antibodies circulate without antigen, as they do in the uninfected state, they continuously bind to and detach from these receptors. However, when the antibodies exist as immune complexes with antigens, they bind to and remain attached to these cells.[6] The presence on the cells' membranes of large numbers of antigen-antibody complexes can alter membrane structure[7] and may interfere with the cytotoxic functions of these cells. Although antibodies provide the body with an adequate defense against most bacteria, they are an inadequate defense against virus-infected cells or tumor cells, which can only be controlled by cytotoxic or killer lymphocytes.

If AIDS is simply the recognition of immunologic aberrations and their resultant diseases in a specific population, which have gone unrecognized in nations with less sophisticated sanitary and medical facilities, then its recognition may present a significant opportunity to improve the state of health of a large segment of the world's population. This theory can be tested by the measurement of immune complexes and by the quantitative and qualitative evaluation of suppressor and helper T lymphocytes in the inhabitants of such countries as Haiti and the nations of equatorial Africa. A decade-by-decade analysis could determine if an absolute increase in suppressor T cells is succeeded by an absolute deficiency in helper T cells as the populations grow older and have been infected longer.

Antigen-antibody complex modification of cellular function can be evaluated in vitro by measuring phagocytosis by macrophages and by measuring target cell cytolysis by killer lymphocytes and cytotoxic T cells previously exposed to antigen-antibody complexes. Should these studies be positive, there is the possibility of prophylactic treatment by plasmapheresis of the blood of persons at high risk for AIDS, excluding those with hemophilia. Patients suffering from viral or parasitic infections or Kaposi's sarcoma might be treated not only by plasmapheresis, but also by harvesting their own killer lymphocytes, cytotoxic T lymphocytes and macrophages and culturing these in growth media to allow the cells to restore free and active Fc receptors. These cells may then be reinjected into the patients.

ARTHUR BERKEN, MD
Clinical Professor of Medicine
SUNY at Stony Brook
Stony Brook, NY 11790

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HOUSE OF DELEGATES

The House of Delegates of the Medical Society of the State of New York will convene from October 14 through 17, 1984 at the New York Hilton. The schedule of sessions, reference and nominating committees, officers, councilors, and trustees, and a report of the House committee on bylaws are presented on pp 417–432 of the August issue of the *Journal*.

Address correspondence to Editor, New York State Journal of Medicine, *420 Lakeville Road, Lake Success, NY 11042. Letters should be typed double-spaced and include the signature, academic degree, professional affiliation, and address of each author. Preference is given to letters not exceeding 450 words, and every effort will be made to assure prompt publication. All letters are personally acknowledged by the Editor.*

Hazards of music and dancing

TO THE EDITOR: I would like to alert readers to a new syndrome I have recently encountered, reflecting "signs of the times."

Two 17 year olds appeared within a week of each other complaining of patchy hair loss at the top of the scalp. History revealed that both had been spinning on their heads while "break dancing" (Fig 1).

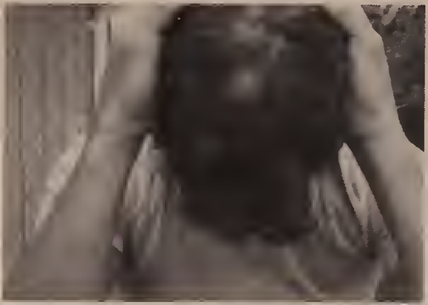

FIGURE 1. Hair loss due to break dancing.

A young woman came to my office several months ago with patchy baldness in a longitudinal distribution at the top of the scalp extending laterally. She had been wearing a wide-banded heavy set of headphones while jogging. Switching to the new light-weight headsets stopped the hair loss.

May I suggest that we add to our medical lexicon, "alopecia walkmania" and "alopecia breakdancia?"

STUART M. COPPERMAN, MD
3137 Hewlett Avenue
Merrick, NY 11566

Replies to "A foreign physician in Russia in the 1930s"

TO THE EDITOR: Fortunate indeed is Dr Julius D. Krombach (1984; 84: 317-318) to be safely retired in Florida, having been successful in emigrating from Berlin to Yugoslavia and then to the Soviet Union. In the Soviet Union he confronted medical problems such as lice and typhus, mosquitoes and malaria, and scarlatina, all without antimicrobials. He learned that he need only cite Stalin to be in the right. This tactic, so opportune, would it have helped him to say "Heil Hitler" and be spared these experiences?

Dr Krombach comments, "The Russian jail was better than a German concentration camp, but only by degrees"—such as crematoria, medical experimentation, mass graves, skin lamp shades, and gold extraction from teeth? Finally, his ship, the *Champlain*, was permitted to enter New York harbor, unlike the doomed vessel carrying thousands of his coreligionists that was refused refuge in Cuba, despite prior agreement. It sailed off the United States shore, hoping for humane intervention by President Roosevelt, but was turned away to a voyage of perdition.

To be alive, to be a survivor, and to join the acceptable scenario of anti-Sovietism, rather than living with memories of the Holocaust, that is solace, but I doubt if it is peace.

HARRY E. BELLER, MD
1010 Persian Lane
Sebastian, FL 32958

TO THE EDITOR: Dr Krombach writes in the June issue of the *Journal*, that he and his family escaped the Nazi Germany crematoria by fleeing to the USSR. There they found safety, and he found a position as a physician in a hospital. After the war, they emigrated to the United States, where the doctor prospered and is now retired in Florida.

This physician attacks with typical "cold war" assertions the country that gave him and his family life. But why the *Journal* opened its valuable pages to this type of unverifiable propaganda clearly deserves an explanation.

HARRY BLOCH, MD
49 Crest Drive
South Orange, NJ 07079

In reply: Most of the letters I have received did not share these writers' sentiments, but I do wish to respond to their comments.

I certainly am very grateful to have been privileged to come and live in the United States; although I could have done nicely without a six-year odyssey through European countries, especially Russia. I left the "Fatherland" rather abruptly, precisely because I would have rather died than raise my arm in a Hitler greeting. Instead I preferred to emigrate into a nebulous future and took my mother and mother-in-law with me as a heavy but welcome burden. My other relatives ended in the Nazi gas chambers. So I know well and grieve about all the horrendous Nazi crimes mentioned. When I stated that "the Russian jail was better than a German concentration camp, but only by degrees," I was intending to describe the medical environment in those years. I will give a brief description: the jail, overcrowded almost entirely with innocent people like myself, was hell. When I was forced into a fairly large cell, big enough maybe for 10 people, I thought I would die from asphyxiation in a short time. I counted 56 unwashed, starving people, expecting to be interrogated and tortured in the night, maybe to die with a bullet in the back of the neck or to be transported to a place in the north of Siberia to work themselves to death. Surely there were some sturdy men who survived the ordeal and returned. I myself was several times called out during the night and shoved into an empty prisoner vehicle; I expected the traditional bullet in the neck any minute. By this time I did not care much, but I was just thrown into another prison under similar conditions.

I can only conclude that Dr Beller is one of the remaining few (I met another such person on a Mexican cruise) who believe that the Soviets still adhere to the communistic ideals—everyone to his capabilities, to everyone according to his needs. There are also some people who believe that the Nazi concentration camps never existed!

Reviewing lately in my mind this turbulent century, I relived my medical experiences in the Russian countryside and wrote down the facts as they occurred. I can see no reason for eternal gratitude to the Soviet Union, which admitted me among other German-Jewish physicians because the country needed well trained physicians badly. I served there to the best of my capabilities, and they repaid me by dumping me for no reason whatsoever in the inferno of their "system of justice." I have indeed been lucky to get out of Russia alive, while other colleagues had to perish there.

JULIUS KROMBACH, MD
PO Box 283
Crystal Beach, FL 33523

Psittacosis pneumonia with cavitation

TO THE EDITOR: Psittacosis varies in its clinical features. Some patients exhibit only a pulmonary infection while others have systemic disease with involvement of the liver, spleen, lymph nodes, or heart. A variety of radiologic patterns can be detected on chest roentgenograms in those patients with pulmonary manifestations.[1,2] Cavitation has thus far not been reported. Here we present a case of systemic psittacosis that evolved into cavitary pneumonia.

Case Report. A 55-year-old man was admitted to the Brookdale Hospital Medical Center with a four-week history of cough productive of a whitish sputum. He had received a seven-day course of doxycycline, which relieved the cough temporarily, but three days prior to admission diarrhea and a more severe cough productive of dark sputum developed. He denied other symptoms. The patient had no prior history of pulmonary disease, smoked four cigars a day for many years, and worked as a public health sanitarian.

On admission the patient was plethoric and had a cough productive of mucoid, green sputum. Examination revealed temperature, 38.9° C; respiration, 36/min; pulse, 84/min; blood pressure, 112/60 mm Hg. Examination of the upper airway revealed a white exudate in the left tonsillar fossa. Examination of the chest revealed dullness to percussion over the lower half of the right lung, with decreased breath sounds of a bronchial quality in that area. The remainder of the physical examination was unremarkable.

Laboratory studies demonstrated an elevated white blood count of 17,800 with 13% band forms, 70% segmented, 12% lymphocytes, and 5% monocytes; hemoglobin, 13.2 g/dL; hematocrit, 38%. A sputum stain showed many white blood cells, predominantly gram-positive diplococci, none of which were intracellular. A chest roentgenogram revealed a dense infiltrate in the middle lobe of the right lung (Fig 1). Other studies including cold agglutinins and febrile agglutinins were negative. The Legionella titer was 1:64. Sputum culture revealed normal flora, blood cultures were negative, and *Candida albicans* grew from cultures of the tonsillar exudate. Serum enzyme levels revealed mild abnormalities, with an elevated SGOT of 61. A liver and spleen scan revealed generalized liver dysfunction and splenomegaly.

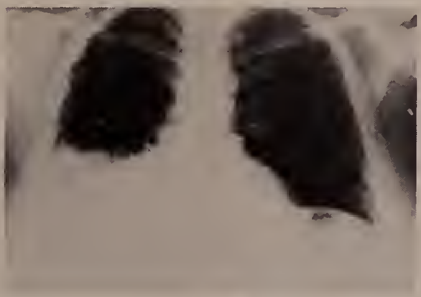

FIGURE 1. Chest roentgenogram on admission.

The patient was treated with intravenous penicillin; however, the fever and leukocytosis persisted, and on the fourth hospital day oral erythromycin therapy was begun. He had not improved by the 10th hospital day; all antibiotics were discontinued. On the 13th hospital day radiologic changes were noted, namely cavitation in the middle lobe of the right lung and the development of a right pleural effusion. Tomography did not reveal bronchial obstruction; fiberoptic bronchoscopy demonstrated inflammation of the orifice of the right middle lobe bronchus. Bronchial biopsy revealed nonspecific inflammation. Bronchial washings showed gram-negative organisms; other studies were unremarkable. The patient was then restarted on intravenous penicillin therapy as treatment for a lung abscess. By the 19th hospital day the patient's temperature and white blood cell count had returned to normal. On further questioning the patient revealed that he had two apparently healthy parakeets at home. Complement fixation for psittacosis was obtained on the 15th hospital day with a convalescent titer obtained on the 25th hospital day. The results were a titer of 1:16 and 1:64, respectively.

Discussion. The diagnosis of psittacosis in this patient is based upon the significant rise in titer. In retrospect he had many of the characteristic features of this disease, namely history of exposure to parakeets, fever, cough productive of nonpurulent sputum, pulse-temperature deficit, hepatosplenomegaly, hepatocellular dysfunction, and a lobar infiltrate on chest film.[3] The peculiar feature of this case was the development of cavitary pneumonia. We believe that the cavitation was a complication of the psittacosis infection because cavitation occurred within the area of consolidation, and cultures obtained from bronchoscopy were negative for bacteria—suggesting no evidence of superimposed bacterial infection as the cause of cavitation.

ARTHUR HALLE, MD
ELLIOTT BONDI, MD
JACK J. ADLER, MD
The Brookdale Hospital Medical Center
Linden Blvd at Brookdale Plaza
Brooklyn, NY 11212

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Physicians in political office

TO THE EDITOR: In reply to Stanley Grant's letter in the June issue of the *Journal* (1984; 84:297-298), I have several comments.

His call for political involvement is inadequate. I do agree that for too long physicians have stayed clear of politics, even when it concerns patient care or physicians' pocketbooks. However, political action committees are not the answer. Politicians are too easily swayed by other influences, if they are not fully committed to an issue or its solution. A person must believe in something to fight effectively for it.

The only real chance that doctors have to effect change and influence the political process is to run for, and win, political offices. This political involvement has to be supported by the medical establishment. We have to search for physician candidates who have a range of political views and are committed to preserving the quality care enjoyed in this country. Coupled with the support of a slate of candidates, we need an intensive public relations campaign to offset the incorrect and misemphasized information pervading the media today.

We have to educate the public ourselves and influence the legislatures by being members of those bodies. If we don't take this route, we are doomed to failure. But time is running out. We must act now.

VINCENT P. GARBITELLI, MD
486 Willis Ave
Williston Park, NY 11596

In reply. Nothing would please the New York Medical Political Action Committee (NYMPAC) more than having physicians run for and win political offices, particularly for the New York State Senate and Assembly.

We have sought such a person and continue to do so. A voice for medicine on the floor of these legislative bodies would provide medicine with the forum for the public relations you mentioned. Such persons have not come forth yet, so we seek out those who do choose to run and express an interest in our concerns and *support* them.

STANLEY J. GRANT
NYMPAC
Medical Society of the State of New York
420 Lakeville Road
Lake Success, NY 11042

Gynecomastia following supradiaphragmatic radiation for lymphoma

TO THE EDITOR: Gynecomastia has been reported in adult men[1] as well as adolescents[2] following combination chemotherapy. Infradiaphragmatic radiation carries a high risk of gonadal damage despite testicular shielding.[3] This report describes an adult with lymphoma who developed painful gynecomastia following supradiaphragmatic irradiation.

Case Report. A 40-year-old man was noted to have a right tonsillar mass in 1974. A tonsillectomy showed diffuse, poorly differentiated lymphocytic lymphoma. Physical examination did not reveal lymphadenopathy or hepatosplenomegaly. Routine laboratory tests and complete staging workup showed no lymphoma elsewhere. The patient was treated with radiotherapy to the right cervical and tonsillar area, as well as to the right axilla and mediastinum. Six months later axillary nodes developed. Biopsy of a left axillary node showed a diffuse, poorly differentiated lymphocytic lymphoma. Treatment consisted of additional local radiation. Subsequent examinations showed no evidence of disease. The patient remained well until about six months later, when he noticed a painful lump in the left breast. He was on no medications, and he had no evidence of liver disease, thyroid disease or other endocrine abnormalities. There was no change in weight. Examination showed a 2 × 1 cm freely movable and tender mass beneath the left nipple. There was no nipple discharge and no other adenopathy or hepatosplenomegaly. A mammogram was inconclusive. An excisional biopsy revealed benign gynecomastia. Since that time the patient has remained free of lymphoma, and there has been no recurrence of gynecomastia.

Discussion. Several conditions have been associated with the development of painful gynecomastia in adult males.[4] Gynecomastia seen in patients with cancer who are on chemotherapy is attributed to direct gonadal damage. Infradiaphragmatic radiation may damage testicular function and cause gynecomastia. There has been no previous description of gynecomastia in patients receiving only supradiaphragmatic irradiation. Localized lymphomatous involvement of the breast is rare.[5] Most patients with lymphomatous breast masses have advanced disease, making the diagnosis obvious.

It is often assumed that any mass occurring in a patient with lymphoma represents the same entity. Benign gynecomastia, although rare in the patient without prior chemotherapy or lower abdominal radiation, has to be considered in the differential diagnosis of breast masses in male patients with lymphoma. Since benign gynecomastia, in contrast to lymphoma of the breast, does not require any specific treatment, we would recommend biopsy of any new breast mass in male patients with lymphoma, who otherwise show no evidence of disease.

ROBERT S. WEINER, MD
The Don Monti Division of Oncology
Department of Medicine
North Shore University Hospital
Manhasset, NY 11030

KLAUS DITTMAR, MD
THOMAS J. DEGNAN, MD
Department of Medicine
Cornell University Medical College
New York, NY 10021

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AMA VOTER REGISTRATION DRIVE

The American Medical Association and the American Medical Association Auxiliary is organizing a voter registration drive on state and local levels for physicians, spouses, family members, and AMA employees. Project MEDVOTE is aimed at encouraging active participation in the 1984 general election.

During the past two years, issues such as diagnosis related groups, hospital staff privileges, professional liability, euthanasia, and third party reimbursement have sparked debate in state and local governments. The officials chosen in the upcoming election will have a voice in shaping the legislation that will address these issues as well as other laws affecting the medical community and the delivery of health care services.

Project MEDVOTE hopes to mobilize the more than 350,000 active members of the AMA and Auxiliary and their associates to register and vote in November. The New York State chairman is Mrs. George Lim.

Lead exposure among iron workers in New York City

A continuing occupational hazard in the 1980s

ALF FISCHBEIN, MD, MICHAEL LEEDS, BS, STEPHEN SOLOMON, PHD

ABSTRACT In order to evaluate the health effects of occupational exposure to lead, we examined 97 iron workers who were engaged in urban demolition and restoration of lead-coated metal structures in the New York City metropolitan area between 1974 and 1982. It was found that more than half of the study group had blood lead levels that exceeded 40 μ/100 mL—the current standard set by the Occupational Safety and Health Administration in 1978 for exposure to inorganic lead. No significant difference in the blood lead levels of these workers was noted before or after 1979. Moreover, elevated blood lead and zinc protoporphyrin (ZPP) levels were found among individuals who were in the immediate vicinity of those workers directly involved in lead burning. We suggest, on the basis of these results, that engineering control and personal hygiene programs be instituted, based on the recognition that a hazard is also posed to such "adjacent workers" commonly not considered as a high risk group. This is particularly crucial since it is anticipated that similar urban renewal projects will occur with increasing frequency in the foreseeable future. We strongly recommend, moreover, that physicians be alert to the possibility of lead poisoning when treating persons in this occupational group.

(NY State J Med 1984; 84:445-448)

INTRODUCTION

Occupational exposure to inorganic lead is common in American industry.[1] In fact, it is estimated that one and a half million American workers face the potential of hazardous lead exposure. Although the greatest risk occurs in the mining and smelting of the metal, there are over 100 other occupations in which lead may pose a health hazard. While improved industrial hygiene and protective measures in the working environment have reduced the number of reported cases with clinical manifestations of acute lead poisoning, adverse effects of excessive lead exposure still occur with appreciable frequency, albeit of a less acute and nonspecific nature.[2]

Evidence has emerged during the past decade to suggest that adverse effects from lead exposure can appear at blood lead concentrations which, until recently, were considered as "safe"[3,4]; as a consequence, many countries, including the United States, have revised the acceptable standard for blood lead levels.[5] Strict enforcement of such criteria has made clinical lead poisoning a rare occurrence in some countries.[6]

We have reported excessive occupational exposure to lead in various industrial settings in the United States.[7,8] The use of oxyacetylene propane torches for cutting iron and steel structures coated with lead-based paints, for example, may generate toxic fumes which, if inhaled, can result in lead poisoning.[9-11] We have reported several cases of lead poisoning among iron workers who dismantled an elevated railroad system in New York City. It was determined that this incident was related to an inadequate respirator system.[12] Subsequently, we were given the opportunity to make additional observations of other iron workers, employed in similar demolition projects in the New York City metropolitan area, primarily in response to the concerns of union officials and some employers. The purpose of the present communication, therefore, is to report on our most recent findings in this group; in addition, we report studies on workers not directly engaged in lead burning, but who may be at a similar risk of hazardous lead exposure due to their proximity to the lead burning operations.

METHODS

Subjects and laboratory determinations. The study group consisted of 97 male iron workers, all members of the International Association of Bridge, Structural, and Ornamental Iron Workers, Local Unions No. 40 and 364, who were employed principally in the demolition of steel and iron structures coated with lead-based paint using oxyacetylene propane torches. The data were obtained from six different work sites located in New York City. Fifty-five workers, employed at more than one location, were examined on several occasions; however, only the data from the first set of observations were included in this analysis. Each subject underwent a comprehensive examination that included occupational and medical histories. On the basis of information obtained in the occupational history, the lead-exposed group was further subdivided into the following categories: (1) 47 individuals, with a mean age of 39.4 years ± standard deviation (SD) of 10.8 years, who used the torches to cut the metal on a full-time basis and were called "burners" (Job B); (2) 28 assistants to the burners, with a mean age of 38.2 ± 13.8 years (Job A); (3) 22 part-time burners, with a mean age of 42.9 ± 9.3 years who performed other tasks at the work site most of the time, but who were also in close proximity to the burners (Job P). In addition to the iron workers, 23 men (mean age of 38.9 ± 12.6 years), employed at a chemical manufacturing plant where

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From the Department of Community Medicine, Environmental Sciences Laboratory (Dr Fischbein and Mr Leeds), and the Department of Neoplastic Diseases (Dr Solomon), Mount Sinai School of Medicine of the City University of New York, New York.

Address correspondence to Dr Fischbein, Assistant Professor, Environmental Sciences Laboratory, Cummings Basic Sciences Building, The Mount Sinai Medical Center, 1 Gustave L. Levy Place, New York, NY 10029.

there was no occupational exposure to lead, were also examined and served as an industrial comparison group. The three subdivisions of iron workers and the control subjects did not differ with respect to age [$(F(3,89) = 0.54$, $P > 0.05$].

Blood lead (PbB) levels were measured by atomic absorption spectrophotometry. The effect of lead on heme synthesis was assessed by measuring the zinc protoporphyrin (ZPP) content in fresh capillary blood specimens using a hematofluorometer.[13,14] Except for 16 workers who were examined at a hospital occupational medicine clinic, all subjects were examined at the work sites.

Statistical methods. The clinical and laboratory data and the occupational history information were encoded for entry into an IBM 370 computer as a catalogued data set, and all calculations were performed using the Statistical Analysis System (SAS) packages. The univariate statistics for each continuous variable were examined, and since the distributions were not normal, nonparametric procedures were used to evaluate group differences (Kruskal-Wallis test with a chi-square approximation as the test of significance). Moreover, intra-group associations were demonstrated by the Spearman rank-order correlation coefficients.

RESULTS

The continua for PbB and ZPP were subdivided into four categories, and the frequency distribution of these variables are presented in Table I. The Occupational Safety and Health Administration (OSHA) blood lead standard for occupational exposure to inorganic lead is 40 μg/100 mL; 50 μg/100 mL is an acceptable level for ZPP. It should be noted that only 41 (42%) of the subjects had PbB concentrations below 40 μg/100 mL, and a comparable number of workers had acceptable ZPP levels. In contrast, 29 (30%) and 9 (9%) of the workers exhibited PbB levels that exceeded 60 μg/100 mL and 80 μg/100 mL, respectively. In one subject, the PbB value was 128 μg/100 mL. Furthermore, 21 (22%) had moderately elevated ZPP levels, while 34 (35%) showed markedly abnormal elevations. Two subjects, in fact, had ZPP levels of 364 and 349 μg/100 mL. The control subjects were all within the acceptable values for both PbB and ZPP.

When the iron workers were categorized with regard to job category, it was observed that 55% of the workers in Job B had elevations of both PbB and ZPP (Table II, Fig 1). Moreover, 70% of those in Job B and 82% of Job P subjects showed elevated concentrations of either PbB or ZPP. It is noteworthy that only 57% of the workers engaged in Job A had normal PbB and ZPP values, and that 29% of them had abnormal levels of both variables. As illustrated in Figure 1, few iron workers had PbB above 40 μg/100 mL while the ZPP level was less than 50 μg/100 mL; the obverse was also true (PbB less than 40 μg/100 mL with ZPP greater than 50 μg/100 mL was uncommon). Seven subjects fell into the former category, five from Job A and two from Job B. When a "discrepancy" between PbB and ZPP was found (Table II), it could be explained by the occupational history, which indicated either brief exposure (elevated PbB with low ZPP) or a history of high exposure in the past (low PbB with elevated ZPP). The seven workers found to have low PbB and elevated ZPP levels were burners.

The mean (± SD) PbB values for Job B, Job A, Job P and controls were 51.5 (± 27.5), 34.9 (± 1.7), 53.5 (± 19.2), and 16.2 (±6.3), respectively; and for ZPP, 99.4 (± 70.7), 50.3 (± 39.8), 130.8 (± 103.1), and 18.7 (± 3.9), respectively. Each subclass of iron workers was above acceptable levels for PbB and ZPP, while the controls were considerably below the upper limits for blood lead and ZPP concentrations. The controls were also a more homogenous group, as illustrated by the comparatively large variances found among the iron worker groups.

Significant differences were found for PbB ($\chi^2 = 8.14$, $P < 0.007$) between Job B and Job A. Similar results were found when comparing Job A and Job P for PbB ($\chi^2 = 10.85$, $P < 0.001$) and ZPP ($\chi^2 = 12.10$, $P < 0.005$). Since the mean PbB and ZPP levels of Job P subjects were the highest and also showed the greatest variability, it is suggested that these individuals may have had considerable direct lead exposure as a consequence of their part-time burning duties. Consistent with this conclusion is the observation that no significant differences in duration of current lead exposure were found between the workers studied. It should be noted that every lead-exposed group had significantly higher PbB and ZPP levels than the controls.

In order to explore the interrelationships between PbB, ZPP and the duration of lead exposure, Spearman correlation coefficients (rho) were computed, and the results are presented in Table III. (When correlations result in probabilities greater than 0.05, the alternative hypothesis is rejected and it is assumed that the value is not significantly different from zero, regardless of the sign of the coefficient.) Significant positive correlations were found for all lead-exposed workers between ZPP and PbB; these were not observed in the control group. Among the burners, ZPP levels were inversely related to hemoglobin (Hgb) levels. Both parameters indicate the effect of lead on the hematopoietic system. In addition, the ZPP and PbB values of the burners (Job B) tended to be higher in men who experienced longer

TABLE I. Distribution of Blood Lead (PbB) and Zinc Protoporphyrin (ZPP) in 97 Iron Workers

PbB (μg/100 mL)	Number of workers	Percent	ZPP (μg/100 ml)	Number of workers	Percent
<40	41	42	<50	42	43
40–59	27	28	50–99	21	22
60–79	20	21	100–149	12	12
≥80	9	9	≥150	22	23
Total	97	100		97	100

TABLE II. Distribution of Blood Lead and Zinc Protoporphyrin Levels by Job Category in 97 Iron Workers

Job Classification	Total Number	Blood lead <40 μg/100 ml ZPP <50 μg/100 ml	Blood lead >40 μg/100 ml ZPP <50 μg/100 ml	Blood lead <40 μg/100 ml ZPP >50 μg/100 ml	Blood lead >40 μg/100 ml ZPP >50 μg/100 ml
Assistant (Job A)	28	16 (57%)	4 (14%)	0 (0%)	8 (29%)
Burner (Job B)	47	14 (30%)	1 (2%)	6 (13%)	26 (55%)
Unspecified (Job P)	22	4 (18%)	3 (14%)	1 (5%)	14 (64%)
Total	97	34 (35%)	8 (8%)	7 (7%)	48 (49%)

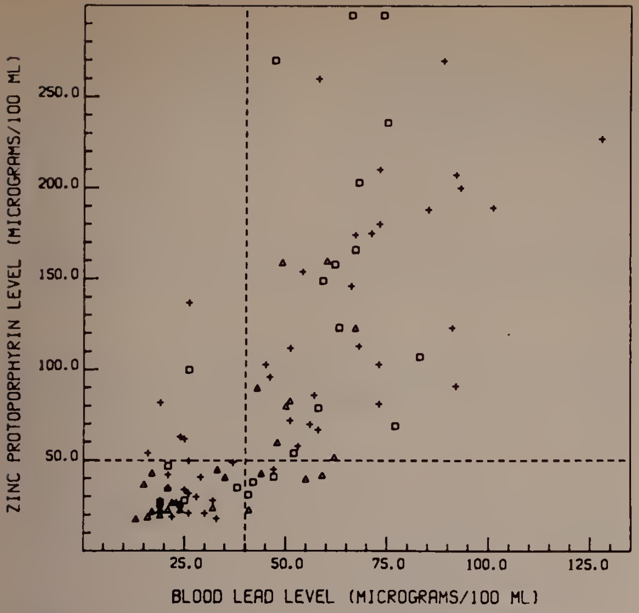

FIGURE 1. Scatter diagram of blood lead and zinc protoporphrin levels in 97 New York City ironworkers. Note that the two highest ZPP observations in the plot, which were actually 360 μg/100 mL and 349 μg/100 mL were beyond the range set for the graphic presentation. □, unspecified ironworker; +, burner; Δ, adjacent worker.

exposures at the work sites, as reflected by the positive correlation coefficients. It should also be noted that ZPP, PbB and Hgb were unrelated in the control group.

DISCUSSION

During the period between 1974 and the early part of 1983, we studied 97 iron workers in the New York City metropolitan area who were engaged in the dismantling and repair of metal structures coated with lead-based paint. More than half of the 97 iron workers examined exhibited significant elevations of PbB and ZPP levels, and this trend was observed at five of six work sites surveyed. Only 57% of the subjects in any given job category had acceptable levels of PbB and ZPP, and all iron workers had significantly higher levels, as compared to an industrial control group. PbB and ZPP levels were important covariates for all lead-exposed individuals, and, for those with direct exposure, ZPP showed a negative correlation with Hgb; PbB and ZPP were directly associated with duration of exposure at the work site.

These observations are in agreement with our initial findings[12] and corroborate our view that there is a continuing health hazard from lead exposure in this population of workers. Moreover, there was no difference in mean PbB and ZPP concentrations between those examined before or after 1979 (Table IV). The OSHA Standard was promulgated in November 1978.

Since the duration of exposure at the various work sites was relatively brief, and we did not have sufficient retrospective information for a repeated measures experiment, we were unable to address the issue of cumulative chronic exposure. The significant correlations, however, between PbB and ZPP suggest that both measures are reliable indicators of the type of exposure experienced by these workers. While PbB concentration is a good indicator of current or recent absorption of lead, ZPP is a more stable, long-term indicator of the effect of lead on the hematopoietic system. ZPP represents the effects of lead on the erythroid cells in the bone marrow, and it remains in the erythrocyte for the life span of the cell.[15] The relationship observed in this population between PbB and ZPP, therefore, is consistent with previous findings.[14,16]

It should be emphasized that elevated PbB and ZPP levels were not limited to those individuals directly involved in the lead burning process, which generated lead fumes from the paint, but were also observed with appreciable frequency among the assistants. It is uncommon for the latter workers to be issued protective respiratory equipment.

TABLE III. Intercorrelation Matrix of Blood Lead (PbB), Zinc Protoporphyrin (ZPP), Hemoglobin (Hgb), and Duration of Exposure (months) for 97 Iron Workers and 23 Control Subjects

Group	Variable	ZPP ρ (*P* value)*	Hgb ρ (*P* value)	Duration of exposure ρ (*P* value)
All workers	PbB	*.789 (.0001)*	−.144 (.2614)	*.216 (.0592)*
	ZPP		*−.357 (.0041)*	*.282 (.0122)*
	Hgb			−.045 (.7684)
Adjacent workers	PbB	*.760 (.0001)*	.225 (.3144)	.240 (.2833)
	ZPP		.090 (.6889)	.301 (.1736)
	Hgb			.416 (.0967)
Burners	PbB	*.771 (.0001)*	.058 (.7168)	*.456 (.0059)*
	ZPP		*−.339 (.0301)*	*.557 (.0005)*
	Hgb			−.258 (.1770)
Unspecified workers	PbB	*.695 (.0003)*	†	.167 (.4700)
	ZPP		†	.126 (.5809)
	Hgb			†
Controls	PbB	−.298 (.1679)	.238 (.2738)	‡
	ZPP		.347 (.1044)	‡

* *P* values ≤0.05 are italicized
† not available
‡ not applicable

TABLE IV. Comparison of Blood Lead and Zinc Protoporphyrin Levels in Iron Workers Examined Before and After 1979.

	Age			Blood Lead Level ($\mu g/100$ mL)			Zinc Protoporphyrin Level ($\mu g/100$ mL)		
Study Group*	Number	Mean	SD	Number	Mean	SD	Number	Mean	SD
Iron workers examined before 1979	43	39.00	12.13	43	42.86	29.20	43	83.98	75.94
Iron workers examined after 1979	27	41.22	9.74	54	50.56	18.96	54	99.00	79.20
Controls	23	38.78	12.64	23	16.17	6.33	23	18.70	3.90

* Analyses of variance were computed with respect to age, PbB, and ZPP. Significant F ratios were found for PbB and ZPP: F (2,117) = 20.20 ($P < 0.0001$) and F (2,117) = 10.81 ($P < 0.0001$), respectively. Duncan's new multiple range test applied to these two variables revealed that the differences between iron worker groups were not significant, but that both subgroups had significantly higher PbB and ZPP levels, as compared to the controls.

It is suggested from these data that cognizance of the potential health hazard to such workers be taken, and that they should be included in any industrial hygiene design for workers engaged in lead burning.

A comprehensive program of engineering controls, personal hygiene, and adequate medical surveillance must be conducted for all such workers. Physicians should be alert to the suspicion of lead poisoning when confronted with an iron worker as a patient. These individuals can exhibit nonspecific symptoms of occupational lead poisoning, as has been reviewed elsewhere.[17,18]

In conclusion, lead poisoning continues to be a problem for iron workers engaged in the demolition and repair of metal structures coated with lead-based paint. It should be emphasized that the burning operation is only one part of such restoration projects. Other work procedures involving significant lead hazards may also be performed by these workers. Iron workers conduct repair and rewiring of bridge cables, for example. In 1983, eight such workers were found to have elevated PbB and ZPP levels, corroborating the findings presented in this study. The PbB concentrations ranged from 31 to 82 $\mu g/100$ mL and their ZPP levels ranged from 41 to 205 $\mu g/100$ mL. The mean (± standard deviation) values for PbB and ZPP were 57 (± 12) $\mu g/100$ mL and 97 (± 38) $\mu g/100$ mL, respectively.

Occupational lead poisoning continues to be a significant health problem in New York State despite a decrease in average blood lead levels found in the United States general population between 1976 and 1980.[19] The newly established New York State Department of Health Heavy Metal Registry received reports of 540 cases of elevated blood lead levels (> 40 $\mu g/100$ mL) in men exposed to lead at the worksite, between December 1, 1981 and November 30, 1982.[20] We anticipate that this problem will persist in the foreseeable future because of urban renewal and modernization projects currently being planned. All workers employed at such work and repair sites must be considered at high risk of lead poisoning.

Acknowledgment. This work was in part supported by National Institute of Envrionmental Health Sciences Grant ES 00928.

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Palliation of unresectable esophageal carcinoma by intraluminal intubation

GIL HAUER SANTOS, MD

ABSTRACT Patients with esophageal obstruction secondary to carcinoma frequently are seen at advanced stages of the disease when only minimal palliation can be offered. For these patients palliation is provided to make it possible for them to swallow and to prevent aspiration of saliva or food into the airways. We present our experience during a period of 10 years with 48 patients with squamous cell carcinoma of the thoracic esophagus, who had an intraluminal prosthetic tube inserted to permit swallowing and avoid aspiration. Eleven patients died in the hospital, and 37 were discharged after surgery that enabled them to swallow satisfactorily.

(NY State J Med 1984; 84:449–451)

INTRODUCTION

Most patients with unresectable esophageal carcinoma will develop esophageal obstruction leading to dysphagia and aspiration of saliva and particles of food. A great majority of these patients are not candidates for a major palliative procedure but can have their symptoms alleviated by the insertion of an esophageal, intraluminal prosthesis that will permit them to drink and eat—at least a blenderized diet—and will decrease aspiration with its associated pulmonary complications. In this study the efficacy of an intraluminal prosthesis in relieving esophageal obstruction was tested on patients with advanced esophageal carcinoma.

PATIENTS AND METHODS

From January 1971 to December 1980, 48 patients at the Bronx Municipal Hospital Center, affiliated with the Albert Einstein College of Medicine underwent palliative surgery for esophageal obstruction secondary to advanced esophageal carcinoma with the insertion of a pull-through intraluminal prosthesis. All the patients, 33 men and 15 women, had a squamous cell carcinoma located in the thoracic esophagus. The criteria for the use of an intraluminal tube were unresectability due to the extent of the tumor, local invasion by tumor, presence of distant metastasis or a combination of these factors. Lack of response or recurrence of obstructive symptoms after radiotherapy or chemotherapy necessitated the use of intraluminal esophageal intubation in 15 cases of this series.

For the majority of patients, preparation for surgery included correction of dehydration and, if indicated, hyperalimentation. In this series an absolute criterion for esophageal intraluminal prosthetic tube implant was the presence of actual esophageal obstruction. No prophylactic tube was inserted prior to the occurrence of obstruction to a soft or a liquid diet.

In 35 patients a Fell[1] tube (made of polyvinyl) was used, in 8 patients a Celestin[2] tube (made of latex with a nylon spiral) was used, and in 5 patients a Mousseau Barbin[3] tube (made of Neoplex) was selected. There were no major functional differences among these tubes; their basic design is similar. All three devices consist of a tube with internal diameters varying from 10 mm to 14 mm and with a dilated portion or funnel that sits over the tumor to prevent it from migrating distally. Their distal portion inside the stomach is sutured to the gastric wall[2] or through the gastric wall to the abdominal wall,[1] as in this series, to prevent it from migrating proximally toward the pharynx. A gastrotomy is required to achieve this fixation. It is also necessary to permit a retrograde esophageal dilatation using Tucker dilators that are passed in order of increasing calibers from the stomach to the pharynx. Retrograde dilatation performed in this way is safer[1] than when dilatation is done through the oral route.[6] In most of the patients in this series a gastrostomy tube was left in place for a few days as a safety measure against gastric distention.

RESULTS

Forty-eight patients with esophageal carcinoma studied in this series had an endoesophageal pull-through prosthetic tube inserted to relieve esophageal obstruction that produced dysphagia, often associated with aspiration. Three of these patients also had a tracheoesophageal fistula, and it was expected that in these cases, the tubes would have the additional benefit of obliterating the fistulas, thereby reducing the passage of saliva and ingested food into the airway. These three patients died in the hospital 6, 10, and 11 days after surgery. No significant decrease of pulmonary aspiration was obtained in these patients, even though the tube was situated in a position to block tracheoesophageal communication. Eight other patients died in the hospital: three with wound infection, dehiscence, and subsequent sepsis; four with massive aspiration; and one with perforation of the esophagus with mediastinitis (Table I).

Thirty-seven patients were discharged and survived from 14 to 155 days (Fig 1). No instance of tube displacement was documented in this group; however, 23 instances of food impaction requiring mechanical removal were noted in 9 patients—seven with Fell tubes and two with Celestin tubes. In this series all patients that had one episode of food impaction would experience others. One patient had five episodes of food impaction that required removal.

The shortest survival times were obtained on patients that had extensive disease with invasive tumors and with the greatest weight loss. The patients with the longest survival times were those with less extensive disease and less weight loss, and those that could have undergone a different procedure were it not for some clinical contraindication, like cardiac disease or advanced age, for more extensive surgery.

DISCUSSION

The goal of the attending surgeon when treating a patient with esophageal obstruction produced by an unresectable carcinoma of the esophagus is to make it possible for the patient to recover the ability to swallow. This would avoid continuous aspiration of saliva and particulate matter by the patient and also permit oral ingestion of food.

Different options to accomplish these results are available. For the patient with a partial obstruction, a course of radiotherapy may provide adequate palliation for a few months. Another possibility that recently became available is the use of chemotherapeutic agents.[7] Prosthetic intuba-

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Address correspondence to Dr Santos, Assistant Professor of Thoracic Surgery, Albert Einstein College of Medicine, 610 Jacobi, 1300 Morris Park Ave, Bronx, NY 10461.

TABLE I. Results of intraluminal esophageal intubation for palliation in a group of 48 patients with unresectable esophageal carcinoma.

Result of Therapy	No. Patients
Discharged from hospital	37
Hospital mortality	
Dehiscence and sepsis	3
Massive aspiration	4
Pre-existing tracheoesophageal fistula	3
Esophageal perforation	1

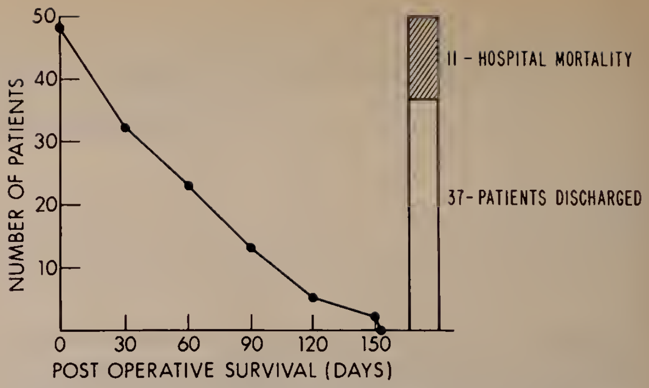

FIGURE 1. Postoperative survival rate after intraluminal intubation of the esophagus in 48 patients with unresectable esophageal carcinoma.

tion can be avoided if there is improvement.

Radiotherapy or chemotherapy should not be considered when the patient has a total obstruction, or if either method has been tried previously. A simple gastrostomy, as advocated in the past, is not a worthwhile procedure, considering that the patient will still be unable to eat or to swallow his own saliva, which will continue to be aspirated into the bronchial tree resulting in pulmonary infection and persistent coughing.

If the patient has an unresectable tumor but can otherwise tolerate a major procedure, I believe that a retrosternal colon bypass is ideal. Patients in this category usually do not have a complete obstruction; therefore, they have not deteriorated into a catabolic state. Whereas a curative or even palliative resection is not possible in this case, a more extensive procedure that provides better palliation can be chosen. A colon bypass does not necessitate a thoracotomy, and when the blood supply of the colon is preserved, it produces excellent results.[8,9] The decision on what segment of the colon to use for a bypass is made at the operating table based on the caliber and blood flow of the left, middle, and right colic arteries. This intraoperative evaluation of the blood supply to the colon was found to be more accurate than the evaluation made before surgery with angiographic studies of the colonic arterial supply as advocated by others.[8,12] I agree with Wilkins and Burke[8] and Postlethwait et al[9] that a bypass made with an isoperistaltic segment of colon gives better results; therefore, I prefer to use the colonic segment supplied by the left colic artery. However, an antiperistaltic bypass will be performed if necessary. As an alternative to colon bypass, several authors advocate a gastric pull-up procedure and have reported good results.[10]

Some patients are so debilitated that they cannot tolerate any extensive procedure, and for them the alternative of an intraesophageal prosthetic tube insertion is available. This procedure should be used as a last resource, and when properly indicated and done with minimal mortality and morbidity, can provide excellent palliation. Mousseau Barbin tubes are the most rigid type and have the potential for early erosion through the esophageal wall.[4] Celestin tubes have a potential for fragmentation when inside the patient for long periods of time, with separation of the nylon spiral and perforation of the bowel as consequences.[5] Fell tubes are easier to work with; however, the surgeon has to be careful to prevent the softer funnel from being squeezed by the tumor or by harder structures outside the esophagus, with compromise of the lumen of the tube.

Intraesophageal tubes can be inserted by two different methods—push through and pull through. In both, the tubes are introduced through the mouth; however, push through tubes are introduced into the esophagus by pushing it from the mouth down, while pull through tubes are inserted by pulling them down into the esophagus through a gastrotomy made for that purpose. The main advantage of the push through tubes is that their insertion does not require a laparotomy, thus avoiding the possibilities of wound infections and dehiscence. Their main disadvantage is the higher incidence of esophageal perforation during esophageal dilatation and also of retrograde displacement[6] due to absence of fixation inside the abdomen.

The advantages of pull through tubes is that they have a larger caliber, are easier to keep patent, and have less tendency to migrate proximally. The recent introduction of Atkinson tubes that incorporate a distal flange to prevent proximal migration may diminish or eliminate this problem.[6,11] The esophageal dilatation necessary for insertion of pull through tubes is also facilitated by performing a retrograde dilatation through the open stomach. The main disadvantage of the pull through technique is related to the necessity of performing a laparotomy and gastrotomy, and the morbidity[11] and mortality that is associated with this procedure when it is performed on a debilitated and emaciated patient.

The postoperative care for a patient with an esophageal intraluminal tube has to be explained in detail to patients. They should restrict their diet to liquids and blenderized or pureed food. A high calorie diet may be necessary. The last part of their meal should consist of half a glass of carbonated water or soda to rinse the debris deposited inside the tube. They should not go to bed for two hours after meals. They should use two or more pillows in bed in order to avoid regurgitation that can occur even in the presence of a competent cricopharyngeus, due to the neutralization of the gastroesophageal junction reflux preventing mechanism.

Esophageal carcinoma is associated with significant anorexia that can be severe enough to make patients avoid ingestion of food even if they are capable of eating. This becomes apparent before total esophageal obstruction takes place or after a patent intraluminal tube is in position. The incidence of airway aspiration of food or saliva was difficult to document, but pulmonary complications with pneumonia were observed in eight patients.

Overall, however, the use of pull through tubes in this study made it possible to restore deglutition in patients with late stage esophageal obstruction resulting from nonresectable esophageal carcinoma, and enabled 37 of 48 patients to be released from the hospital.

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PEER REVIEW ORGANIZATION IS SELECTED

The Empire State Medical, Scientific, and Educational Foundation, Inc has been chosen as the peer review organization (PRO) for New York State. This action is in accordance with the 1982 federal Peer Review Improvement Act which requires that such an organization be established in each state to oversee hospital care provided to Medicare patients. At present, the review process is conduced by 17 professional standards review organizations.

The PRO, to be located in the Medical Society's headquarters on Long Island, will operate through four subcontractors: Island Peer Review Organization, Inc; New York County Health Services Review Organizations; Adirondack, Hudson, Mohawk Medical Peer Review Organization, Inc; and Empire State Peer Review Organization, Inc.

The organization's responsibilites will include a review of random cases requiring hospitalization or outpatient treatment of Medicare patients. The information will be used to determine whether the quality of care and utilization of hospital facilities conform to statewide norms.

MSSNY PROGRAM FOR IMPAIRED PHYSICIANS

Governor Cuomo has signed into law a bill that enables the Medical Society of the State of New York to expand its program for assisting physicians impaired by drug dependence, alcohol abuse, or mental illness. The program, developed in association with the State Health Department, is aimed at identifying physicians in the state with such problems, arranging for and monitoring treatment, and providing rehabilitation services. Funding for the program will be supplied through a $10 surcharge on physicians' licensing fees.

The law ensures that individual case records will be confidential and that the physicians handling the cases will be immune from civil suits. Cases in which a physician refuses treatment or presents a hazard to the public will be reported to the Office of Professional Medical Conduct of the State Health Department.

Thrombocytopenia in a 34-year-old woman with chronic depression

CASE PRESENTATION

Susan Fitzmaurice, MD (Intern, Department of Medicine): A 34-year-old white woman was admitted with shortness of breath, easy bruisability, abdominal cramps, ocular pain, and weakness for three to five days' duration.

Thirteen years earlier, several months after the birth of her only child, she developed a psychotic illness, initially diagnosed as postpartum depression and later as manic-depressive psychosis. She was initially treated with lithium carbonate and thioridazine; after approximately 10 years of this therapy, she developed what appeared to be nephrogenic diabetes insipidus and hypothyroidism. Lithium was discontinued, and she was treated with sodium levothyroxine.

Approximately two and a half years prior to the present admission, she was admitted to the National Institutes of Health (NIH), where all drug therapy was discontinued, with later introduction of chlorduline, a drug then under study, with only questionable response in her psychotic condition. Approximately six months thereafter, she was started on carbamazepine, which she judged to be the only effective medication for her condition. However, she continued to be severely depressed, and nortriptyline therapy was begun two months prior to the present admission; the dosage was slowly increased to an adequate blood level during the several weeks prior to admission.

During the week prior to admission, she had noted a tooth infection together with occasional constipation, polydypsia, and polyuria. During the three to four days immediately preceding admission, she noted shortness of breath on exertion, weakness, dizziness, abdominal cramps, retroocular pain, and easy bruisability. She had noted one episode of vaginal bleeding following coitus four weeks earlier, but denied any gastrointestinal bleeding, hemoptysis, hematuria, fever, or chills. Current medications included thioridazine, carbamazepine, levothyroxine, nortriptyline, and possibly tetracycline for vaginal pruritus.

When seen by her psychiatrist, her hemoglobin was 6.1 g/dL; hematocrit, 16%; platelet count 5,000/mm^3. She was immediately referred to the hospital emergency department, where the hematologic findings were confirmed. In addition, the peripheral blood smear revealed occasional schistocytes and spherocytes. The total white blood count, differential count, serum electrolyte levels, and prothrombin time were normal.

The patient's medical history was otherwise unremarkable. The patient consumed alcohol only occasionally and had smoked two packs of cigarettes per day for many years.

The patient's father and one brother suffered with depressive illnesses.

Physical examination on admission revealed a blood pressure of 120/84 mm Hg in the supine position and 106/76 mm Hg in the upright position. The pulse was 124/min in both positions; the respiratory rate was 16/min; and the temperature was 100.6°F. Her skin was pale and showed numerous petechiae and ecchymotic areas. The conjunctivae were pale; the fundi were not remarkable. Jugular venous distention was present; there were a few freely moveable small cystic areas in both breasts. A soft I/VI systolic ejection murmur was audible over the entire precordium. Abdominal, pelvic, and rectal examinations were negative; the stool Guaiac test was negative. There was no adenopathy. The patient's mood was somewhat labile; the neurologic examination was negative.

Laboratory examinations on admission revealed a hemoglobin of 6.1 g/dL, a hematocrit of 17.6%, and a white blood cell count of 8,000, with 62% polymorphonuclear leukocytes and 29% lymphocytes. The platelet count was 5,000/mm^3; the prothrombin time was normal. The serum fibrinogen level was 264 mg/dL (normal range, 200 to 400 mg/dL); the direct and indirect Coombs' tests were negative. The urine was normal on examination and was negative for hemosiderin. The electrocardiogram revealed sinus tachycardia, a first degree arteriovenous block, and nonspecific ST and T wave changes. The chest film was within normal limits.

Immediately on admission, a hematology consultation was obtained and a diagnostic procedure performed. Intravenous fluids, prednisone, an antacid, blood transfusions, and fresh frozen plasma were administered in an effort to maintain a hematocrit level of 25%. In view of her low-grade fever, blood cultures were drawn. Shortly after admission, the patient received acetylsalicylic acid, dipyridamole, and daily plasmaphoresis via an external jugular line. Because of increased agitation, she was also started on thiothixene; levothyroxine was continued.

On the third hospital day she was given 20 units of platelet transfusions and transferred to the intensive care unit. Shortly thereafter she sustained a tonoclonic seizure, and an emergency computed tomography (CT) scan of the

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Based on the clinicopathologic conference (CPC) held at Long Island Jewish-Hillside Medical Center, New Hyde Park, NY, on October 14, 1983.

Moderator: Marc Yunis, MD, Department of Medicine.

Clinical Discussion: Steven Carsons, MD, Assistant Professor of Medicine, SUNY at Stony Brook; *Pathology Presentation:* Anastasia Anagnostopoulos, MD, Department of Pathology, Long Island Jewish-Hillside Medical Center.

Editor: JOHN T. FLYNN, MD.

Address correspondence to Dr Flynn, Consulting Editor, *New York State Journal of Medicine*, PO Box 5404, 420 Lakeville Road, Lake Success, NY 11042.

head showed a hypodense area in the right frontal lobe consistent with an old infarct; no fresh bleeding or localized mass was detected. Phenytoin therapy was begun, the dose of acetylsalicylic acid was increased, and thiothixene was discontinued.

On the fourth hospital day, the total serum bilirubin was 4 mg/dL, but thereafter returned to normal. The blood glucose became elevated in the range of 200 to 425 mg/dL, and the patient was treated with insulin.

On the fifth hospital day, the patient became agitated and pulled out the plasmaphoresis catheter. The catheter was reinserted, 7 units of platelets were administered, and the patient was started on dextran. Despite the platelet transfusions, the platelet count never increased beyond 44,000/mm^3, and for most of the hospital stay, remained below 20,000/mm^3. The hematocrit remained between 25% and 35%; reticulocyte counts ranged from 5% to 12%; the differential white blood cell count remained normal. The prothrombin time and partial thromboplastin time remained within normal limits. The serum lactate dehydrogenase (LDH) remained elevated throughout, between 1,225 and 2,155 U/L (normal range, 60 to 200 U/L); the serum glutamic-oxaloacetic transaminase (SGOT), alkaline phosphatase, cholesterol, and serum electrolyte levels were normal throughout. During the final three hospital days, the blood urea nitrogen remained in the range of 35 to 40 mg/dL; the serum creatinine remained normal.

On the seventh hospital day the patient required amobarbital to control her agitation; her temperature rose to 104°F; the white blood cell count was 15,400. After cultures were drawn and a lumbar puncture performed, with normal spinal fluid findings, the patient was begun on oxacillin and gentamicin. On the following day, the patient vomited coffee-ground material and was given cimetidine and three packed red blood cell transfusions; platelet transfusions were ordered, but before they could be administered, the patient sustained cardiac arrest and could not be resuscitated.

Blood culture reports received after the patient's death indicated growth of gram-positive cocci, identified only as *Staphylococcus.*

CLINICAL DISCUSSION

Steven Carsons, MD (Physician-in-Charge of Clinical Immunology): The death of this woman resulted from an acute disease that involved profound anemia, thrombocytopenia, fever, and an apparent organic brain syndrome accompanied by seizures. She had a long history of psychiatric illness and treatment with multiple psychopharmacologic agents.

Before considering the most likely cause of these symptoms, I would like to review some other possible causes, if only to indicate the reasons why they seem to me to be unlikely. Most recently she was given carbamazepine, a drug with a capacity for profound bone-marrow suppression. Her total and differential white blood cell counts, however, appeared to be normal. Even correcting for reticulocytosis, she appeared to have an active bone marrow with an appropriate reticulocytosis. So I do not consider her condition to represent an instance of carbamazepine-induced bone marrow suppression.

Rarely, an aleukemic form of leukemia may present with a coagulopathy; and, in the presence of extensive bone marrow replacement, there can be extreme anemia and thrombocytopenia. However, in this case there was no evidence of blasts on the peripheral smear nor of abnormal cellular morphology in the leukocyte series. I will not consider the possibility of leukemia further.

Could this patient have had an autoimmune disease affecting the hematologic system? In Evans' syndrome, autoimmune hemolytic anemia and thrombocytopenia are prominent features, usually with a positive Coombs' test; the direct and indirect Coombs' tests in this case, however, were both negative. The patient was transfused extensively soon after admission, and I assume that there was no difficulty with cross-matching; so apparently there were no significant anti-red blood cell antibodies—neither isoantibodies nor autoantibodies.

Perhaps the most significant finding in the hematologic picture of this patient is the presence of schistocytes on the peripheral smear. Abnormalities of red blood cell morphology should always be looked for in anemia, as was done in this case. Their presence suggests the occurrence of a process known as microangiopathic hemolytic anemia.

Microangiopathy can occur with renal vascular lesions, especially those associated with malignant hypertension. This patient had indications of diabetes insipidus and some mild non-specific abnormalities on urinalysis; however, there was no evidence of extensive renovascular disease. Microangiopathy can also occur with heart disease, especially with aortic valve disease, and in association with endocarditis. This patient was febrile, had clubbing of the fingers and a systolic murmur, and had a history of a tooth infection; she was alleged to have had staphylococci in her blood culture. And yet, there is no convincing evidence of organic heart disease. The normal chest film and the relatively normal electrocardiogram do not suggest such a process. The non-specific systolic murmur, I will have to assume, was secondary to flow characteristics of the anemia. An anemia, with a hematocrit of 16% and associated with endocarditis would presuppose a long-standing infection.

Red blood cell fragmentation and thrombocytopenia are prominent factors of the syndrome of disseminated intravascular coagulation usually presenting as a consumption coagulopathy, with extensive derangements in the coagulation parameters. However, the normal prothrombin time speaks strongly against the occurrence of disseminated intravascular coagulation.

In 1925, Eli Moschkovitz described a syndrome of hemolytic anemia, thrombocytopenia, renal disease, fever, and changing mental status, terminating in coma, in a series of patients from the New York area.[1] This syndrome is now known as thrombotic thrombopenia, or thrombotic thrombocytopenic purpura (TTP). This patient had many of the expected findings of this condition—a microangiopathic hemolytic anemia, red blood cell fragmentation, a severe thrombocytopenia, fever, and an organic brain syndrome associated with seizures. The clinical syndrome of TTP results from the occlusion of small arterioles and capillaries with platelet plugs. Periodic acid-Schiff-positive material, indicative of glycoprotein, and material identified as fibrin by light microscopy and immunofluorescence are also present. These occlusive lesions can occur diffusely, so that the syndrome may have a degree of heterogeneity. This patient did not have significant azotemia or renal disease, but this is not a consistent feature of TTP. In addition, perhaps to a degree generally underrecognized, the coronary arteries may be involved, and patients may either die of acute myocardial infarction or develop conduction-system abnormalities. It is worth noting that this patient had a prolonged P-R interval on the electrocardiogram.

The cause of TTP is unknown; perhaps because of its association with systemic lupus erythematosus and other autoimmune diseases,[2] it is assumed that this disease has an immunologic basis. In such patients, however, there is no consistent clinical evidence of immunologic derangement. Mant et al[3] in 1972 described deposits of immunoglobulin M and of the third component of complement (C3) in lesions of patients with TTP; usually, however, there is no consistent elevation in serum immune complexes or depression in serum complement. That this disorder occurs in HLA-identical siblings suggests that a genetic factor is involved. That it has occurred in a husband-and-wife pair and in small geographic clusters suggests an environmental cause, perhaps an infectious agent. Infusions of fresh frozen plasma accompanied by plasmaphoresis appear to induce remissions—a notable advance in the treatment of this disorder, which suggests that a plasma factor may be missing or may be abnormal. It is likely that all of the above factors are relevant; significant information may reside in the study of the molecular pathology of platelet- and endothelial-cell glycoproteins, such as fibrinogen, fibronectin, Factor VIII, and von Willebrand factor.

Presentations at recent clinical research meetings report the finding of high molecular weight von Willebrand factor multimers in the plasma of patients with the closely related hemolytic-uremic syndrome.[4]

In this case, diagnostic procedures of choice would be either a gingival biopsy, which in about 40% of cases reveals the lesions associated with TTP; or a bone-marrow aspiration biopsy, which I prefer, because it would be very important at the early stage of the illness to rule out a drug-induced bone marrow suppression or perhaps a leukemia.

Now, let us refer to the patient's other medical problems. This patient had a long history of psychiatric illness that started after the birth of her first child. She developed diabetes insipidus and hypothyroidism while on lithium therapy and certainly had evidence of a urinary concentrating defect on admission. Lithium is widely reported to cause both hypothyroidism and diabetes insipidus. The former is due to a blockage of hormone release, and the latter occurs probably because of a toxic effect on the renal tubules. Consideration of these factors could explain all of the patient's medical problems, some possibly drug-related. Before doing so, however, one should attempt to develop one unifying diagnosis or at least have one unifying theme for discussion.

Lithium-induced hypothyroidism, as mentioned, is caused by a blockage of hormone release. Should not this be reversible with discontinuance of ingestion of the drug? Most sources of information agree that it is reversible.

Should not the diabetes insipidus secondary to lithium also be reversible, especially over the course of several years after discontinuance of the medication? My colleagues in the Department of Psychiatry indicated that in most cases diabetes insipidus due to lithium is reversible.

Is the finding of previous brain infarct on CT scan consistent with the patient's final moribund neurologic state?

Could this patient have had an autoimmune disorder initially manifested by immune thyroiditis, interstitial nephritis, and cerebral vasculitis, which could have accounted for the previous infarct and perhaps for the earlier psychiatric manifestations? As is often true with immune diseases, a chronic immune disorder with a heterogeny of manifestations might have terminated in a fulminant TTP-like syndrome.

Edward Hotchkiss, MD (Attending Physician): I would like to emphasize that the findings at the National Institutes of Health never firmly established the presence of nephrogenic diabetes insipidus in this patient. The information suggests that she probably had psychogenic polydipsia; procedures to confirm a tubular defect could not be completed. She drank enormous quantities of water, while not taking lithium, often 17 liters per day. She sat with a glass of water at all times and was drinking from it continuously.

In addition, she had a rather unusual manic-depressive illness; her hospitalization at the NIH for about 18 months was characterized by rapidly cycling depressive periods. The cycles were predictable and occurred at a frequency much greater than one would expect in the common variety of manic-depressive illness. The suspicion would be that there was some kind of chemical or neurologic basis different from that seen in the usual manic-depressive illness. Her reported response to carbamazepine is in line with this notion; she felt that medication was a lifesaver. She came out from the pit of despair seemingly under miraculous control, as she put it, while on this drug. She indicated that her life had been a misery prior to its administration.

Dr Carsons: Your comments would tend to underscore the atypical nature of what would be assumed to be a lithium-induced defect.

Arnold Blumberg, MD (Director, Medical Services, Hillside Division, LIJ-HMC): There are a few points that might be mentioned here. First, lithium-induced nephrogenic diabetes insipidus may often not be reversible.[5] In 28% of the cases that we have followed, and that were treated with lithium for any period of time, hyposthenuria, which was not reversible with vasopressin, has been noted.[6]

The second point is that her manic-depressive illness started with her pregnancy; subsequently, it proved to be unremitting and predominantly a depressive condition, not manic. She was treated with several drugs under study at the NIH prior to the prescribing of carbamazepine. The story of her being well controlled with carbamazepine is not true; in fact, she had been doing very badly and had been started on an additional drug, nortriptyline, in increasing doses. When she first came to see me, she was getting worse and it was thought that the nortriptyline was responsible. In retrospect, she was probably getting worse all along. She had a fairly steady course, rather than one with acute exacerbations.

E. Meilman, MD (Chairman Emeritus, Department of Medicine): Was an antinuclear antibody titer done? Were any immune complexes looked for?

Gregory Ackert, MD (Chief Medical Resident): Not as far as we know.

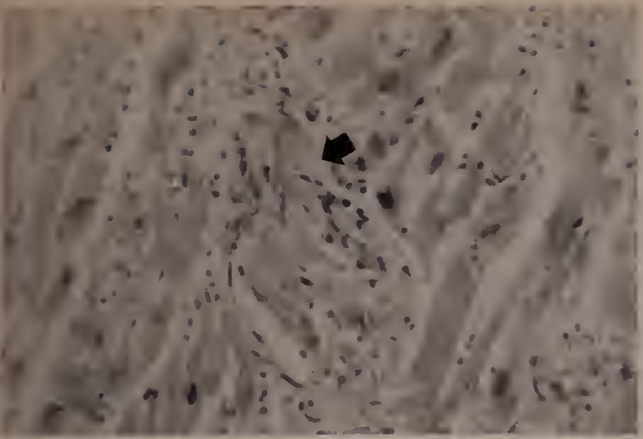

FIGURE 1. Focal destruction of wall of partially thrombosed myocardial vessel (arrow) due to fibrin which is extruded, leading to surrounding inflammatory reaction. (hematoxylin and eosin stain; original magnification × 40)

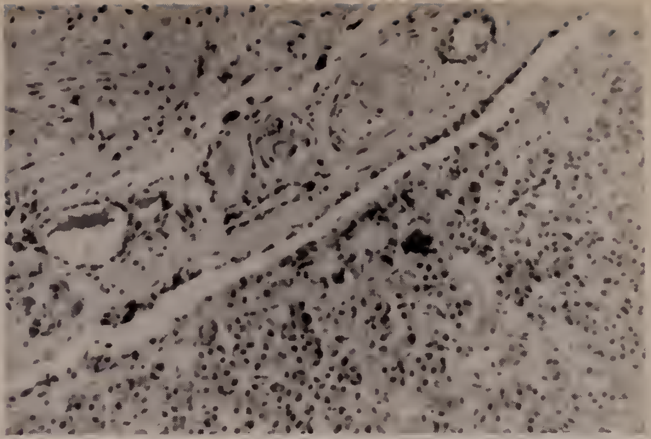

FIGURE 3. Thrombosed vessels at junction of posterior lobe (upper left) and anterior lobe (lower right) of pituitary. (hematoxylin and eosin stain; original magnification × 10)

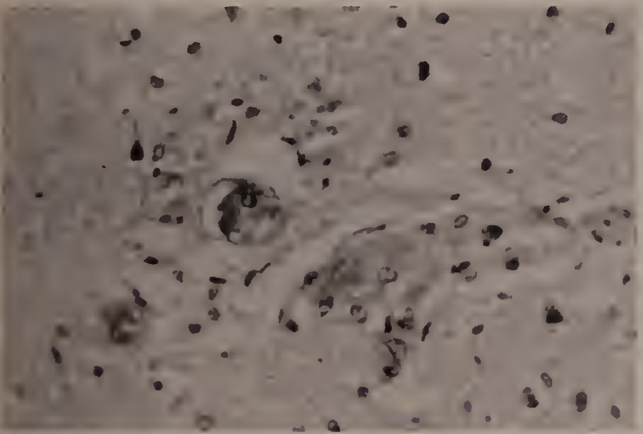

FIGURE 2. Thrombosed vessels within brain. (hematoxylin and eosin stain; original magnification × 40)

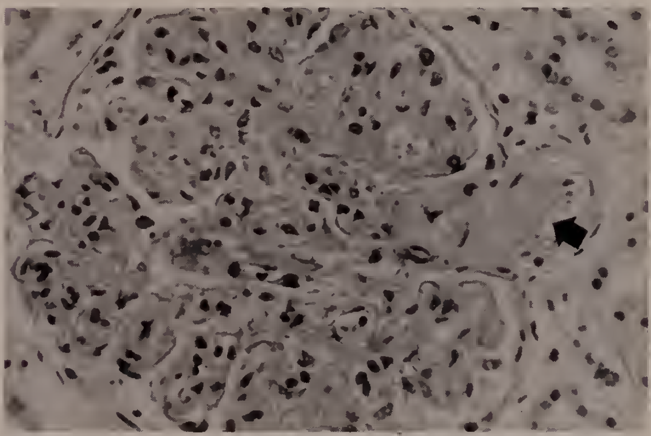

FIGURE 4. Fibrin thrombus within afferent arteriole of renal glomerulus (arrow). (hematoxylin and eosin stain; original magnification × 40)

CLINICAL DIAGNOSES

Thrombotic thrombocytopenia purpura, of undetermined etiology, possible secondary to an underlying autoimmune disorder.

Hypothyroidism secondary to autoimmune thyroiditis.

Depressive psychosis, probably postpartum, treated with lithium chloride, with possible drug-induced diabetes insipidus.

Healed infarction, left cerebral hemisphere.

PATHOLOGY PRESENTATION

Anastasia Anagnostopolous, MD (Pathology Fellow): At post mortem, nearly all the organs showed marked pathologic changes. The most severely affected were the brain, the heart, the kidneys, the pancreas, and the gastrointestinal tract. Microscopic examination showed endothelial proliferation in the capillaries, the arterioles, and the small arteries. Fibrin thrombi were partially obstructing those vessels. There was no histologic evidence of arteritis.

On gross examination of the heart, small petechial hemorrhages and areas of fibrosis were seen in the epicardium, myocardium, and endocardium. Microscopic analysis revealed areas of recent hemorrhage and fibrosis, as well as areas of myocardial necrosis with collections of neutrophils. Within the lumina of the small arteries, non-occlusive hyaline thrombi were intermixed with swollen, prominent endothelial cells. In some areas, disruption of the vessel wall and a surrounding inflammatory reaction could be seen (Fig 1).

Histochemical stains were performed to identify the nature of the thrombi. The periodic acid-Schiff stain yielded a strong positive, but the phosphotungstic acid-hematoxylin stain was not contributory. Also, immunoperoxidase stains for fibrin and Factor VIII were both strongly positive. The Factor VIII stain is preferentially taken by endothelial cells and platelets.

Recent hemorrhages and areas of necrosis adjacent to the obstructed arteries were also seen in the brain (Fig 2), pituitary (Fig 3), kidneys (Fig 4), gastrointestinal tract, and spleen. In the pancreas, the islets of Langerhans were more severely affected than the remainder of the organ.

The bone marrow was hypercellular, with increased numbers of megakaryocytes and red cell precursors. One vessel occluded by a fibrin thrombus was seen on a section taken from the lumbar vertebrae.

The above postmortem findings, plus the clinical history and the findings in the peripheral blood, confirm the diagnosis of thrombotic thrombocytopenic purpura.

In the differential diagnosis, collagen-vascular disease was ruled out in the absence of any evidence of vasculitis. The hemolytic uremic syndrome, which presents clinical and histologic findings similar to those of TTP, occurs most commonly in children, and its most prominent clinical feature—uremia—was absent in this case.

TTP is a rare entity of unknown etiology and of incompletely defined pathogenesis. Of the different theories concerning its etiology, none is completely proven.[7]

The cause of death in this case was severe gastrointestinal bleeding, due to severe hemorrhagic gastritis. Other clinical problems of interest in this patient were diabetes insipidus and hypothyroidism. Both were considered to be side effects of lithium intake over many years. On postmortem examination, no specific changes were found in the kidneys or in the neurohypophysis to explain the three-year history of diabetes insipidus. In the kidneys, the renal tubules had undergone postmortem autolysis, and histologic evaluation was not possible; the chronic changes seen in the cortex were non-specific. On the other hand, the thyroid gland showed histologic changes compatible with lithium thyroiditis, as has been described in the medical literature.[8] The thyroid gland weighed 7.8 g; microscopically, there was marked fibrosis with foci of small thyroid follicles, occasionally dilated and completely depleted of colloid. The lining cells in these follicles were columnar in configuration and in some areas completely filled the lumen of the follicle. The thyroid stroma was infiltrated by lymphocytes. No lymphoid follicles and no proliferation of oxyphil cells (oncocytes) were noted.

Dr Blumberg: Do you feel that the severity of involvement of the kidney was more or less than would be expected, in comparison to the degree of involvement of the other organs?

Dr Anagnostopoulos: It was less involved.

Dr Blumberg: That is an important fact to be emphasized. The so-called "nephrogenic diabetes insipidus," producing an enormous volume of urine—up to 15 liters per day—might have had a protective effect. One piece that was missing from the TTP picture was the absence of azotemia, with a normal serum creatinine to the very end. That would be unusual according to the textbook picture of TTP. I wonder if the presence of the extreme polyuria had a protective action, sparing the kidneys by flushing them out.

Dr Anagnostopoulos: We can only speculate.

Sergio Schwartzman, MD (Resident Physician): What was the correlation of the postmortem findings with the CT scans of the head?

Dr Anagnostopoulos: We did not find any previous lesion of the brain.

David J. Mayerhoff, MD (Resident Physician): Was the bone marrow biopsy that was done during life helpful in any way diagnostically?

Dr Anagnostopoulos: No, because no fibrin thrombi were seen in the vessels.

Nora Varsano, MD (Attending Physician): Can you tell the difference between a burned-out autoimmune thyroiditis and the histologic picture of lithium damage to the thyroid which you presented here?

Dr Anagnostopoulos: The histologic picture that I presented is consistent with thyroiditis secondary to lithium therapy. There was no evidence of Hashimoto's thyroiditis in this case. However, from the histologic picture alone, I do not think that you can rule out a burned-out autoimmune Hashimoto's thyroiditis.

Dr Meilman: It would be extraordinary to have a burned-out Hashimoto's thyroid gland that weighed only 7 g. The ingestion of thyroid substance over so many years probably explains the small size of the gland.

Leonard B. Kahn, MBBCh (Chairman, Department of Laboratories): In most cases of burned-out thyroiditis, you usually can find a few oxyphil cells; I have never seen a complete burn-out comparable to the findings presented here. It is possible, but I wouldn't say that this was likely to be the picture of post-thyroiditis atrophy.

Dr Blumberg: In connection with a possible relation of this whole disease process to a drug, I reviewed the medical literature and spoke to the representatives of the pharmaceutical firm that manufactures carbamazepine. They knew of no case on record of thrombotic thrombocytopenia purpura secondary to carbamazepine. There are some vague descriptions of autoimmune disease with phenytoin, and therefore by extension carbamazepine might be suspect, although the two drugs are not related chemically.

Final Diagnoses

Thrombotic thrombocytopenic purpura, of unknown etiology, with vascular endothelial proliferation and fibrin thrombi, affecting the brain, heart, kidneys, urinary bladder, stomach, colon, pancreas, skeletal muscles, spleen, pituitary, and adrenal glands.

Severe gastrointestinal bleeding secondary to hemorrhagic gastritis.

Lithium-associated thyroiditis.

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Disseminated infection with *Trichosporon beigelii*

ARIF S. EL-ANI, PHD, NIEVA B. CASTILLO, MD

Trichosporon beigelii **is** a yeast that is known as the causative agent of white piedra, a fungal infection of the hair shaft. It is an inhabitant of the soil that is occasionally encountered among the normal flora of the human skin and mouth.[1,2] Recently, however, it has been reported as the cause of either localized[3] or disseminated infection.[4-6] We report on a patient with myeloproliferative syndrome in whom a disseminated infection with *T beigelii* developed. The problems encountered in the diagnosis of this infection are discussed.

CASE REPORT

A 23-year-old man was admitted to Roswell Park Memorial Institute on May 10, 1982 for a bone marrow transplant. He was referred by a physician from Mississauga Hospital, Ontario, Canada, with a diagnosis of megaloblastic anemia. He was diagnosed as having myeloproliferative disorder. He was treated with trimethoprim and sulfamethoxazole in combination, nystatin, allopurinol, and high-dose cytosine arabinoside (Ara-C) for six days. Bone marrow biopsy after treatment revealed a markedly hypocellular marrow with predominantly mature red blood cells. When fever spikes up to 40°C developed, the patient was started on chemotherapy that included tobramycin, carbenicillin and vancomycin. As fever continued, amphotericin B therapy was instituted, and white blood cell (WBC) transfusions were given. He responded favorably and was afebrile for two weeks, after which all antimicrobial agents were discontinued. Because of continued bone marrow aplasia, the patient was considered for bone marrow transplant. Transplant conditioning was done with cyclophosphamide, antithymocyte globulin and total body irradiation. On July 7, 1982, the patient received a T-cell depleted marrow transplant from his father. Two days later he developed fever spikes. A blood culture grew *Staphylococcus epidermidis* and *Candida parapsilosis*. The patient was started on tobramycin, carbenicillin, cefamandole nafate, vancomycin, amphotericin B and ketoconazole therapy. After 30 days of treatment he improved and all antibiotics were discontinued.

On August 11, 1982, the patient was reinfused with a T-cell depleted marrow transplant from his father. Four days later he developed fever, chills, diarrhea and generalized erythematous skin rashes. A skin lesion was biopsied and reported as candidiasis. Chemotherapy with amphotericin B was restarted. The patient's renal function deteriorated, and he died on August 26, 1982. A week prior to his death, *T beigelii* was isolated from blood, urine and bone marrow. *T beigelii* grew from postmortem lung, spleen and kidney cultures. It grew rapidly on Sabouraud's dextrose agar at both room temperature and at 37°C, producing cream-colored colonies that became yellowish, wrinkled or folded within two weeks. Microscopic analysis showed true- and pseudo-hyphae, blastoconidia and arthroconidia. All fermentation tests for *T beigelii* were negative. The organism did not assimilate nitrate. It hydrolyzed urea and assimilated dextrose, sucrose, lactose, maltose, cellobiose, galactose, D-xylose and trehalose.

Autopsy revealed widespread necrosis involving the lungs, kidneys, diaphragm, spleen, liver, cervical and thoracic lymph nodes,

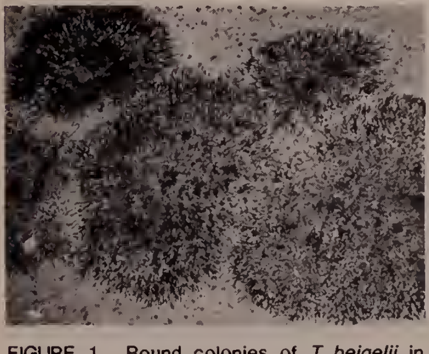
FIGURE 1. Round colonies of *T beigelii* in spleen (methenamine-silver stain; original magnification × 50).

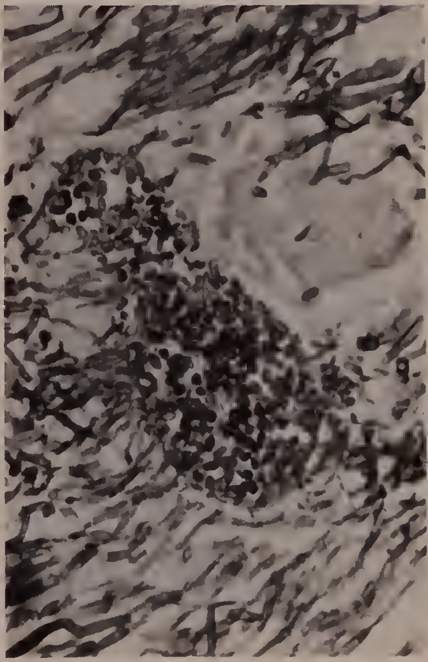
FIGURE 2. A cluster of globose to ellipsoid blastoconidia and septate hyphae in kidney (methenamine-silver stain; original magnification × 480).

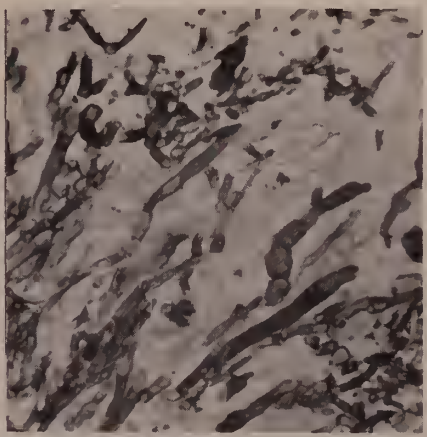
FIGURE 3. Broad septate hyphae with blastoconidia and fine pseudo-hyphae arising from chains of blastoconidia in kidney (methenamine-silver stain; original magnification × 480).

From the Departments of Laboratory Medicine (Dr El-Ani) and Pathology (Dr Castillo), New York State Department of Health, Roswell Park Memorial Institute, Buffalo, New York.

Address correspondence to Dr El-Ani, Senior Cancer Research Scientist, Department of Laboratory Medicine, Roswell Park Memorial Institute, 666 Elm Street, Buffalo, NY 14263.

thyroid gland, pancreas, brain, myocardium and skin with disseminated fungal infection. Microscopic examination showed thrombosed blood vessels invaded by fungal hyphae. The discrete, round fungal colonies (Fig 1) stained more distinctively with Gomori methenamine-silver than with periodic acid-Schiff or hematoxylin and eosin stain. Each colony consisted of conidia and septate, but sparsely branching, hyphae in a radial arrangement. The differentiation between blastoconidia and arthroconidia was not always feasible. In certain colonies, however, clusters of globose to ellipsoid conidia (Fig 2) suggestive of blastoconidia were observed. Rarely were blastoconidia seen attached to hyphal branches (Fig 3). It should be noted that the arthroconidia are not considered a yeast form, as they were described in some recent literature.[5]

DISCUSSION

Disseminated infection with *Trichosporon* is relatively rare and invariably afflicts an immunosuppressed host. It may be confused with candidiasis because of the close resemblance between *Trichosporon* and *Candida* in host tissue. A case in point is the skin lesion from this patient that was biopsied and diagnosed as candidiasis. According to Evans et al,[5] the two genera can be differentiated by the width of their respective hyphae which measures up to 10 microns in the former and rarely exceeds 4 microns in the latter. Another distinction is the formation of round, discrete colonies by *Trichosporon* (Fig 1), and the presence of arthroconidia. However, culture confirmation is always necessary for this infection.

Because *Trichosporon* is a normal inhabitant of the mouth and skin and a contaminant encountered in certain clinical specimens, an infection by *Trichosporon* is often overlooked or diagnosed belatedly. However, as pointed out by Haupt et al,[7] repeated isolation of *Trichosporon* from the mouth, skin and urine of the immunosuppressed host may be a sign of systemic infection.

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EDITOR'S NOTE

Roswell Park Memorial Institute's bone marrow transplant center was closed in April 1983 after a fungal infection was shown to be responsible for the deaths of four patients. A review of patients' charts since the center opened in April 1982 revealed an increased rate of aspergillus infection in patients undergoing bone marrow transplants.

Aspergillus, an organism commonly found in soil, was isolated in the center's air filtration system. Demolition and construction projects in the area may have enabled the fungus to become airborne and enter the hospital's air filters. The immunosuppressed state of bone marrow transplant patients, due to radiation and drug therapy, makes them susceptible to infection with organisms such as aspergillus.

Following renovations, the center should reopen early in 1985.

Mycetoma in post-radiation pulmonary cavities

ELIZABETH CANCROFT, MD, DANUTA MONTORFANO, MD, OSVALDO FULCO, MD

Saprophytic fungi, commonly members of the aspergillus species, can colonize preexisting pulmonary cavities. This has been reported frequently in cases of healed tuberculosis, sarcoidosis, and histoplasmosis, and rarely has been associated with neoplasms, abscesses and pulmonary infarctions.[1-6] It has been reported in patients with ankylosing spondylitis in whom pleuropulmonary involvement with apical pleural thickening develop.[7] Although the occurrence of a mycetoma in cavities produced by radiation fibrosis is alluded to in an extensive review of the literature by Bardana[8,9] in 1980, we could find no detailed case report in our search of the literature.

Two cases of aspergilloma in cavities that developed following radiation therapy are presented. At the time of diagnosis of aspergilloma, the patients were asymptomatic and were being followed because of their prior malignancy.

CASE REPORTS

Case 1. A 60-year-old woman was evaluated initially for the presence of right cervical and right axillary masses. Biopsies of these lymph nodes revealed metastatic undifferentiated carcinoma with squamous and glandular features. Extensive workup to establish a primary site demonstrated the presence of a 1.5 to 2 cm radiographic density in the apex of the right lung and no other

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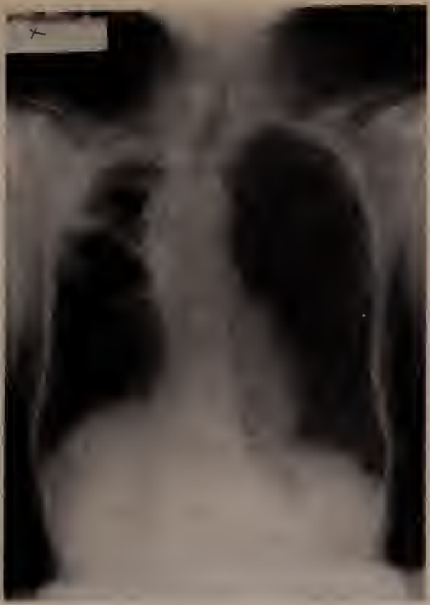
From the Departments of Radiology (Drs Cancroft and Montorfano) and Medicine (Dr Fulco), Nassau County Medical Center, East Meadow, New York and SUNY at Stony Brook, New York.

Address correspondence to Dr Fulco, Attending Physician, Pulmonary Division, Nassau County Medical Center, 2201 Hempstead Turnpike, East Meadow, NY 11554.

abnormality. A total of 5,000 rads in five weeks was delivered to the mediastinum, right supraclavicular region, and right axilla, with an additional 1,000 rads in one week to the supraclavicular region. The patient was relatively asymptomatic and her condition was followed with periodic chest radiograms. Approximately two years after treatment, a chest film revealed an area of cavitation with a mass in the upper lobe of the right lung. Examination of the sputum revealed *Aspergillus fumigatus*. There was a moderate to strong reaction in a gel precipitin test with multiple *Aspergillus fumigatus* antigens. The patient continued to have minimal symptoms until cough, pain, and hemoptysis prompted hospitalization in January 1982. Repeat chest radiograms, linear tomography, and computed tomography (CT) of the chest demonstrated findings consistent with an intracavitary fungus ball (Fig 1). The patient underwent an upper right lobectomy for control and treatment of hemoptysis. The lung specimen was free of tumor recurrence and contained an aspergillus mycetoma. There was no vascular invasion. Culture of the lung specimen grew *Aspergillus fumigatus*; no other organisms were found. The patient did well for several months; subsequently bilateral bronchopneumonia developed and she died. Autopsy revealed no tumor or aspergilloma.

Case 2. A 65-year-old woman had had a left radical mastectomy 13 years earlier for carcinoma of the breast, which was followed by radiation therapy to the supraclavicular, axillary, and internal mammary lymph node chains to a dose of 5,000 rads in five weeks. The patient remained asymptomatic. Periodic chest films showed radiation changes in the upper lobe of the left lung. A chest film in May 1981 demonstrated a cavity with an air crescent in the upper lobe of the left lung. A subsequent chest film in May 1982 showed an enlarging intracavitary mass, and a CT scan of the chest demonstrated an intracavitary mass (fungus ball) (Fig 2).

The diagnosis of aspergilloma was suggested by the radiologic appearance of the lesion and the presence of a moderate to strong reaction in a gel precipitin test with multiple aspergillus antigens on two different occasions. This patient is essentially asymptomatic apart from a cough and is under close observation.



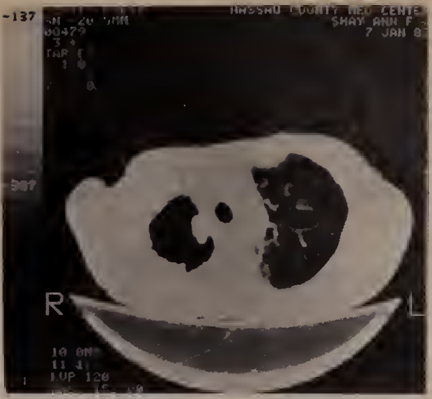
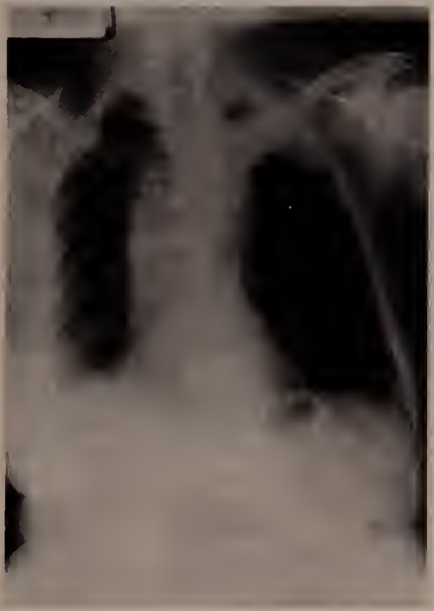


FIGURE 1. Case 1: Left, posteroanterior view of chest showing a density within a cavity in the upper lobe of the right lung; Above, computerized tomography demonstrating an intracavitary fungus ball.



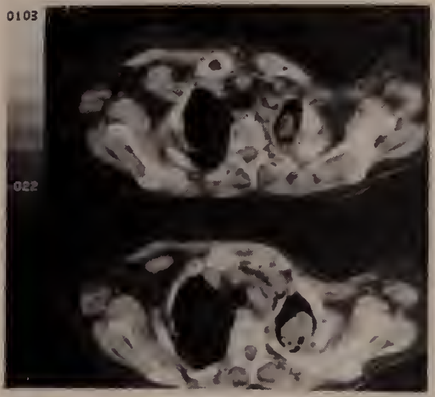


FIGURE 2. Case 2: Left, Posteroanterior view of the chest showing a density within a cavity in the upper lobe of the left lung; Above, computerized tomography confirming the presence of a fungus ball.

DISCUSSION

The first reported cases of human aspergillosis are attributed to Sluyter[10] in 1847 and Virchow[11] in 1856. In 1939, Deve[12] used the term aspergilloma to describe the mycetoma produced by the aspergillus species. Other fungi have been found to colonize cavities: *Coccidioides immitis*, penicillium species and *Allescheria boydii.*

A fungus ball is considered a saprophytic growth inside a preexisting cavity with poor drainage. Tuberculosis is the most common antecedent condition, sarcoidosis the second.[6,8,9] *Aspergillus* may cause pulmonary infarction that may evolve to cavitation. The organisms then form a fungus ball within the cavity which invades blood vessels and adjacent lung parenchyma.

Radiation-induced changes in the lungs can be divided into acute radiation pneumonitis becoming apparent between two and six months after therapy, and a later stage at six months[13] or more, dominated by dense fibrosis and thickening of the alveolar walls with development of cystic and bronchiectatic changes. The incidence and the degree of severity of the changes are dependent upon several factors including the total dose, rate of delivery, and the volume of the lung irradiated. Libshitz and Southard[14] report from their experience that radiation pneumonitis may occur with doses between 3,000 and 3,500 rads and is usually visible at doses above 4,000 rads. The association of pulmonary aspergilloma with post-radiation cavities has not been emphasized or documented sufficiently.

Neilson[15] reported one case of pulmonary aspergillosis in a patient who received radiation therapy following simple mastectomy for carcinoma. An estimated dose of 6,200 rads in three weeks was given to the supraclavicular region and axilla with tangential fields over the chest wall. The patient had a preexisting large, thin-walled cyst in the right lung. Approximately 18 months later because of uncontrolled infection within the cyst, a right lower lobe lobectomy was performed. The pathologic specimen contained masses of fungi within the bronchogenic cyst and the surrounding parenchyma which were identified as *Aspergillus fumigatus.*[15]

The diagnosis of aspergillosis by laboratory methods often presents problems. Sputum cultures may be of limited value as not uncommonly there is no bronchial communication. The ubiquitous nature of the fungus in decaying vegetation, soil, and air makes the significance of its presence in clinical specimens at times uncertain. Other aspergillus species such as *A versicolor*, *A flavus*, *A niger* and *A nidulans* have been reported as possible causes.

A variety of different immunologic techniques have been used to detect or measure antibodies to the genus *Aspergillus.* These include primary binding tests that can be qualitative or quantitative. Sensitive measurement of total humoral as well as class-specific immune responses to a variety of aspergillus components is possible with these quantitative studies. Other in vitro laboratory tests such as immunodiffusion, immunoelectrophoresis and complement fixation provide means of detecting aspergillus antibodies as they relate to clinical disease. A comprehensive discussion can be found in the paper by Bardana.[8,9]

The diagnosis of an intracavitary mycetoma can be suggested by a parenchymal radiodensity surrounded by an air crescent (Monod's sign) on the chest film. The fungus ball is not fixed to the cavity wall and, depending on its size, its position can be changed by obtaining films with the patient in a decubitus position. Although the roentgenographic appearance is quite typical, it must at times be distinguished from other entities that may have a somewhat similar appearance—abscess, inspissated clot within an abscess, necrotic tumors, pulmonary hydatid cysts, liquified infarcts, bronchial adenoma, Rasmussen's aneurysm in a tuberculous cavity, sclerosing hemangioma, sarcoma, hamartoma, and hematoma.[16,17]

Frequently, films of the chest and linear tomography will adequately demonstrate the intracavitary fungus ball. As pointed out by Breuer et al,[18] the use of CT may more definitively demonstrate a mycetoma that is not apparent on plain films or with conventional tomography. In the first case presented here, the CT more graphically demonstrated the changes within the cavity and the fungus ball.

It is important to consider this entity in patients with prior carcinoma who were treated with radiation therapy and to institute appropriate tests to establish the diagnosis and to avoid attributing the radiographic changes to tumor recurrence.

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Cavitary pulmonary metastases in a patient with adenocarcinoma of the colon

LEONARD B. WEINSTOCK, MD, DARRON R. BROWN, MD, DONALD R. BORDLEY, MD

Cavitation may occur in pulmonary nodules caused by neoplastic, infectious, or granulomatous disease, leading to a confusing clinical and radiologic picture. We describe a patient with colonic carcinoma who had a resection three years previously, and in whom pulmonary nodules developed that cavitated during seven days.

CASE REPORT

A 69-year-old retired fireman was admitted for evaluation of productive cough and lung nodules noted on a chest film. He was known to have thalassemia minor and chronic lymphocytic leukemia diagnosed 10 years previously and never treated. A Dukes B, moderately undifferentiated adenocarcinoma of the sigmoid colon was treated with partial sigmoid resection three years before admission. Stool examination for occult blood and sigmoidoscopy performed at six-month in-

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Address correspondence to Dr Bordley, Assistant Professor of Medicine, Department of Medicine, Rochester General Hospital, 1425 Portland Ave, Rochester, NY 14621.

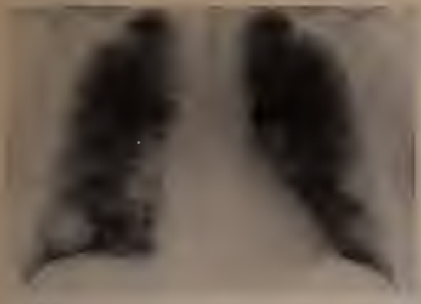

FIGURE 1. Chest x-ray film showing lung nodule in each lung.

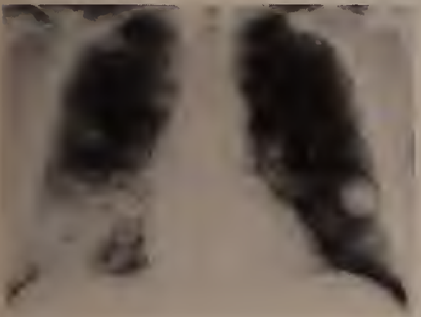

FIGURE 2. Chest x-ray film taken one week after Fig 1 film, showing two cavitary nodules in right lung and persistence of left lung nodule.

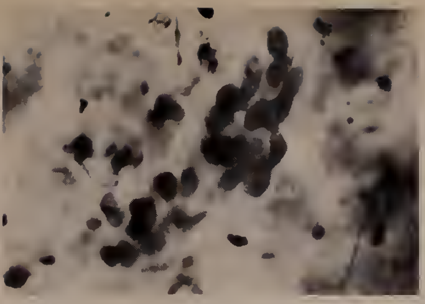

FIGURE 3. Needle aspirate of cavitary lung nodule showing cluster of elongated cells with nuclear abnormalities, consistent with adenocarcinoma (Papanicolaou's stain, original magnification × 700).

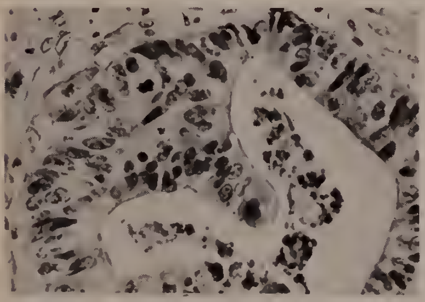

FIGURE 4. Histologic preparation of moderately undifferentiated adenocarcinoma, showing tall columnar cells with pleomorphic nuclei (hematoxylin and eosin, original magnification × 350).

tervals revealed no evidence of disease recurrence.

Nine weeks before admission, he developed a low-grade fever, night sweats, and a cough productive of thick, yellow, odorless sputum. One week before admission, he noted wheezing, dyspnea with exertion, anorexia, and malaise. A chest film showed a solid nodule in each lung, each approximately 4 cm in diameter (Fig 1).

He was admitted with worsening dyspnea and cough. His blood pressure was 146/80 mm Hg; rectal temperature, 38.5 °C; heart rate, 80 beats/min; and respiratory rate, 24/min and labored. His skin was pale. Expiratory wheezing was heard in the right upper and left lower lung fields both anteriorly and posteriorly. Heart, abdomen, neurologic system, and extremities were normal. The rectal examination was normal and revealed no occult blood.

Hematocrit was 29% with a mean corpuscular volume of 61 μm^3. Microcytosis and hypochromia were noted on blood smear. White blood count was 23,600/mm^3 with 58% mature lymphocytes, 25% segmented neutrophils, 5% bands, 2% metamyelocytes, 5% monocytes, and 3% eosinophils. Arterial blood gas measures on room air were pH, 7.45; Pco_2, 35 mm Hg; and Po_2, 57 mm Hg. Gram's stain of the patient's sputum showed many segmented neutrophils and pleomorphic gram-negative coccobacilli.

A chest film on admission (Fig 2) showed two cavitary lesions in the right lung and persistence of the left-lung nodule. Sputum culture yielded a heavy growth of *Hemophilus influenzae*. Bronchoscopy directed by fluoroscopy did not provide a diagnosis, and three sputum cytologic studies were negative. Needle biopsy of the left lung nodule yielded mucin-negative, moderately undifferentiated adenocarcinoma (Fig 3). Histologic appearance was similar to that of his original colon cancer (Fig 4).

He was treated with ampicillin and aminophylline, his cough and dyspnea improved, and he was discharged after two weeks. Because he had no symptoms related to his malignancy, no specific therapy was given.

DISCUSSION

Major diagnostic considerations in patients with cavitary lung nodules include tuberculosis, abscess, Wegener's granulomatosis, fungal infections, and neoplastic disease. While cavitation of primary lung tumors occurs not infrequently (in 3.6% to 29% of cases in one reported series), cavitation of pulmonary metastases is much less common.[1-3] In a study of 5,727 consecutive cancer patients, 314 cases of pulmonary metastases were identified; only four showed evidence of cavitation.[4] In another study of 6,729 consecutive cancer patients, 398 cases of pulmonary metastases were found; 16 showed evidence of cavitation.[5] Though they are uncommon, cavitary metastases are an important diagnostic consideration, particularly in patients with known malignant disease, as in the case reported here. Neoplasms most often reported to cause cavitary lung metastases are those of the cervix, colon, esophagus, pancreas, and larynx, and of the opposite lung.

There are several proposed mechanisms for the development of cavitation in pulmonary metastases. Tumors may outgrow their nutrient supply, leading to central necrosis. Vascular invasion with subsequent thrombosis and necrosis may occur. Hematogenously spread metastases may obstruct small bronchi, leading to air trapping by a ball-valve mechanism; subsequent growth of the tumor around the trapped air may then give an appearance of central cavitation on x-ray examination.

This case illustrates the need to consider metastatic disease in the differential diagnosis of pulmonary cavitation.

Acknowledgment. Shirley A. Van-Duzer-Strachan provided technical assistance in preparing the photomicrographs.

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Water intoxication, hyperpyrexia and rhabdomyolysis in a patient with psychogenic polydipsia

YECHEZKEL SIDI, MD, SIDNEY GASSNER, MD, URI SANDBANK, MD, GIDEON KEREN, MD,
JACK PINKHAS, MD

Healthy subjects or patients with psychogenic polydipsia can consume large amounts of water without having a marked change in blood osmolality.[1] In the rare reported cases of spontaneous water intoxication in patients with psychogenic polydipsia, it appears that the intoxication resulted from resetting of the osmoreceptors controlling antidiuretic hormone (ADH) secretion.[2] People who maintain abnormally high water intake are vulnerable to water intoxication in conditions leading to an increase in plasma ADH concentration; the source of ADH may be endogenic or exogenic. In the following report we describe a patient with psychogenic polydipsia in whom water intoxication developed in association with hyperpyrexia. We propose that the hyperpyrexia may serve as the stimulus for ADH secretion causing water intoxication.

CASE REPORT

A 42-year-old construction worker, apparently previously healthy, was admitted in a state of deep coma. He had spent five hours (between 10 am and 3 pm) on the beach (temperature and humidity data for the day in question are given in Table I) and had engaged in mild noncompetitive physical activity. During this period of time he drank large quantities of tap water and additional quantities of water on his way home. Shortly afterwards he complained of violent headache; two hours later he started to convulse, and within minutes he lost consciousness.

On admission he was in deep coma, without signs of dehydration. The skin was warm and dry. The rectal temperature was 39.5°C; there were no focal neurologic deficits or neck stiffness. Results of pertinent laboratory tests on admission were as follows: BUN 5 mg/100 mL, creatinine 0.75 mg/mL; potassium 3.1 mEq/L, sodium 115 mEq/L, chloride 78 mEq/L, serum osmolality 242 mosm/kg, urinary osmolality 450 mosm/kg, urinary sodium concentration 102 mEq/L, creatinine phosphokinase 19,500 IU, arterial blood pH 7.16, bicarbonate 10.6 mEq/L, hemoglobin 14.2 g/100 mL, WBC count $22.5/mm^3$ with a shift to the left. The findings on cerebrospinal fluid examination were normal as were the excretions of delta aminolevulinic acid and porphobilinogen. The chest films demonstrated bilateral lung densities compatible with the diagnosis of adult respiratory distress syndrome (Fig 1). The sweat sodium and chloride concentrations were normal.

Treatment consisted of an intravenous administration of 5% sodium chloride, sodium bicarbonate, potassium chloride, and furosemide. Severe hypoxemia with PaO_2 of 45 mm Hg on FI O_2 1.0 necessitated endotracheal intubation and artificial ventilation with positive end-expiratory pressure of 10 cm H_2O. Despite correction of the electrolyte imbalance, attained after 24 hours, the patient remained unconscious four additional days. Serum creatinine was never more than 1.0 mg/mL during hospitalization, and creatinine clearance determined seven days after admission was 118 mL/min. Further laboratory results, including aldolase of 56 sigma units (normal 2 to 8 sigma units) and an electromyographic examination, confirmed the existence of severe skeletal muscle injury, albeit without clinical signs or symptoms. Examination of a muscle biopsy specimen with electron microscopy showed clumping of mitochondria that contained crystalloid structures of undetermined nature (Fig 2,3). Additional tests excluded a deficiency of cortisol, aldosterone, renin, or thyroxine that could explain the hyponatremia. An electromyographic examination performed three months after his recovery disclosed no abnormalities.

On recovery, the patient weighed 76 kg, which was his regular weight. The fluid balance during the first week of hospitalization revealed that on admission the patient had been in a state of marked fluid excess (Table II). Psychiatric examination as well as his previous history disclosed that the patient is a compulsive water drinker who easily consumes about 10 L of water every day. On this regimen he regularly excreted 7 to 8 L of urine with an osmolality of 63 to 80 mosm/kg. The serum sodium after recovery was in the range of 137 to 140 mEq/L. A hypertonic saline infusion test and an injection of ADH, after a dehydration that lasted 17 hours,[3] revealed that the patient did not suffer from partial ADH deficiency. The findings on intravenous pyelography were normal.

DISCUSSION

We assume that the patient described suffered from coma and convulsions as the result of water intoxication, although we cannot exclude some degree of sodium depletion due to sweating. This was proved by the marked serum hyponatremia and hypoosmolality as well as the extreme fluid overload documented on the first days of hospitalization. The patient was completely asymptomatic before hospitalization, and hyponatremia was never found within a year of subsequent follow up, during which he continued to consume unusually large amounts of water. We thus conclude that this event of water intoxication happened without previous renal dilution defect. Since the workup did not reveal any other possible ectopic sites for ADH secretion, we can assume that the water

TABLE I. Meteorologic Data, Day of Hospitalization

	Hour					
	10–11	11–12	12–1	1–2	2–3	3–4
Dry temperature (°C)	36.8	38.6	37.6	35.6	35	34.5
Wet bulb temperature (°C)	18.9	19.2	19.8	19.8	19.0	18.5
Discomfort index* (°C)	27.8	28.9	28.9	27.7	27.0	26.5

* Discomfort index = $\frac{\text{dry temperature + wet bulb temperature}}{2}$. Very hard environmental conditions are determined whenever this index is higher than 27°C.

From the Department of Medicine "D" (Drs Sidi, Pinkhas), the General Intensive Care Unit (Dr Gassner), the Casper Institute of Pathology (Dr Sandbank), the Heller Institute, Sheba Medical Center (Dr Keren), Sackler School of Medicine, Tel-Aviv University, Beilinson Medical Center, Petah Tikva, Israel.

Address correspondence to Dr Pinkhas, Head, Department of Medicine "D," Beilinson Medical Center, Petah Tikva 49100, Israel.

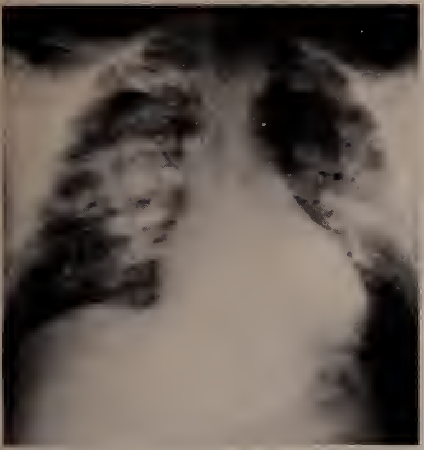

FIGURE 1. Chest film demonstrating bilateral lung densities.

intoxication was the result of a transient increase in ADH secretion by the neurohypophysis.

The water intoxication was accompanied by hyperpyrexia. Considering the lack of evidence for infection, we propose that the hyperpyrexia resulted from the prolonged exposure to a hot environment. However the measured rectal temperature was not high enough and his physical activity was not strenuous enough to justify a definite diagnosis of heat stroke. Regardless of the cause of hyperpyrexia, we suspect that it played an important role in generating the water intoxication in this patient. Normal or increased sodium concentration is usually found in heat stroke patients; decreased serum sodium concentration is rare.[4] The level of hyponatremia observed in this patient is unique. Previous studies in human subjects exposed to heat without dehydration,[5] in pigs exposed to a hot environment leading to an increase in body temperature of 39° to 43°C,[6] and in perfusion experiments in isolated hypothalamic preparations in rats,[7] disclosed that heat, either directly or through dilatation of peripheral blood vessels with relative hypovolemia, stimulates ADH secretion. Previous studies have shown that even a minimal increase in ADH concentration can result in a very marked decrease in free water clearance by the kidneys.[8] We propose that in the present patient, whose water intake was not controlled by thirst, the hyperpyrexia led to a transient increase in ADH secretion, which was inappropriate in respect to plasma osmolality, and that this caused water intoxication.

Another unusual feature in this patient is the laboratory finding compatible with severe muscular damage or rhabdomyolysis. There are several possible explanations for this phenomenon. It can be the result of the convulsions, which is one of the leading causes of rhabdomyolysis, ending in some cases even in acute renal failure.[9] The occurrence of minimal skeletal muscle injury is a common feature in the majority of heat stroke patients,[10,11] whereas severe injury occurs in those with acute renal failure.[12] In addition, hyponatremia by itself has been proposed as a cause for rhabdomyolysis.[13,14] However, the features revealed in this patient by electron microscopic examination are unusual and as yet unexplained; we are not aware of similar findings in reported cases of heat stroke. Although calcium phosphate crystals have been found in the striated muscle,[15] and mitochondrial damage has been suggested by electron microscopic examination[16] in patients suffering from rhabdomyolysis, the ultrastructural picture is different from the one we observed. It is possible that the crystalloid structures found in the mitochondria of our patient are the result of mitochondrial membrane rearrangement. Con-

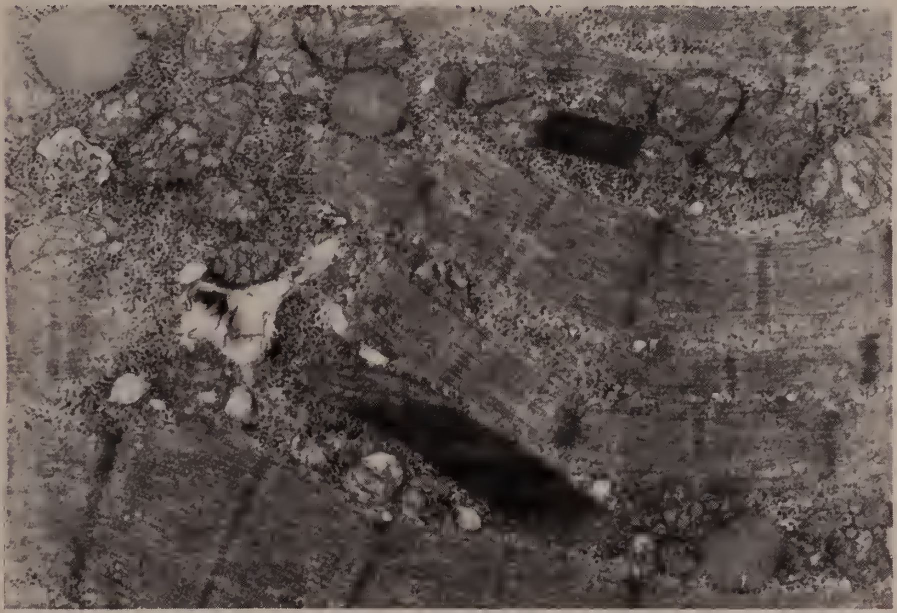

FIGURE 2. Electron micrograph of subsarcolemal enlarged mitochondria with crystals in matrix (original magnification X 22,000).

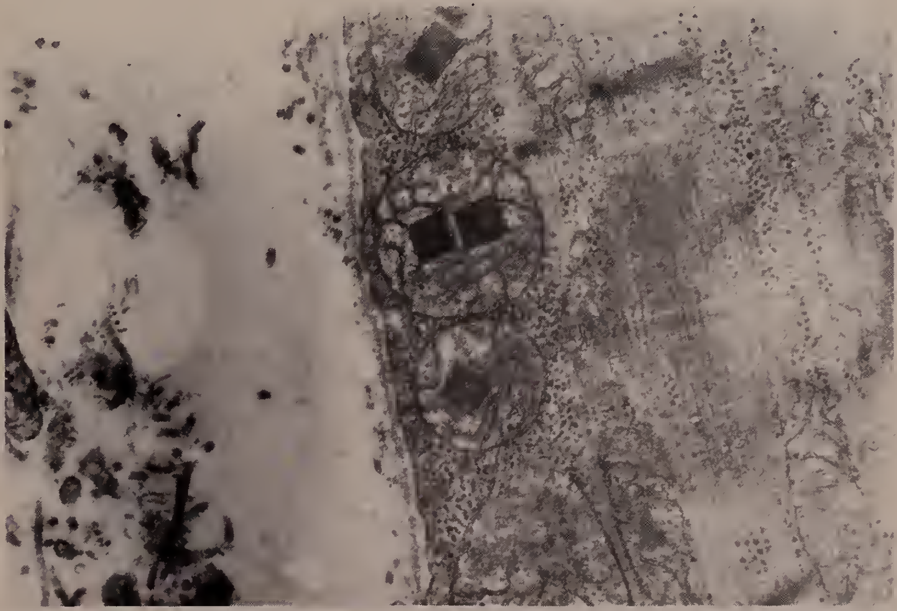

FIGURE 3. Electron micrograph of mitochondria containing crystals between myofilaments. Abundant glycogen granules (original magnification X 18,000).

sidering the lack of electron miocroscopic descriptions of striated muscle biopsy specimens in patients with heat stroke or in hyponatremic patients with severe muscle damage, any further statements linking the muscle findings to the heat stroke or hyponatremia would be speculative. The clinical picture and laboratory findings in this patient are quite bizarre, the report of this unusual combination may draw attention to its occurrence in other similar cases.

TABLE II. Fluid Balance During the First Six Days of Hospitalization*

	Hospitalization Day						
	1	2	3	4	5	6	Total
Urinary output (L/24 hr)	2.5	15.75	6.1	2.7	6.14	2.3	35.49
Input (L/24 hr)	2.5	6.5	2.5	3.5	3.4	1.7	20.1

* The balance indicates a deficit of 15.39 liters. Insensible fluid loss and fluid loss in respiration not included.

Acknowledgments. We wish to thank Professors E. Sohar and D. Danon for their help in the investigation of this patient.

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Fatal toxoplasmosis of the central nervous system in a heroin user with acquired immunodeficiency disease

SHANTHA K. MURTHY, MD, RAYMOND P. SMITH, MD, NITA PARIKH, MD,
ALDONA L. BALTCH, MD, MONICA BISHOP, MD

Acquired defects of T-lymphocyte subpopulations are associated with the development of opportunistic infections and Kaposi's sarcoma among homosexual men, heterosexual intravenous drug abusers and hemophiliac patients, as well as children and sexual partners of some recognized patients.[1-4] We describe a patient with acquired immune deficiency syndrome (AIDS) who died after toxoplasmosis of the brain developed.

CASE REPORT

A 36-year-old heterosexual white, male heroin user was transferred to the Albany VA Medical Center (AVAMC) on June 26, 1981, with a two-month history of 40-pound weight loss, anorexia, malaise, fever, and recent onset of bizzare behavior. A lumbar puncture performed elsewhere during an eight-day hospitalization showed no abnormalities. At AVAMC his temperature was 38°C, weight 143 pounds, and the physical examination was unremarkable. An outline of his clinical course, laboratory data and therapy is given in Table I and Figure 1.

Appropriate cultures were obtained and treatment with antimicrobial agents was begun. The patient continued to be febrile (daily peak temperatures 39°C). Extensive bacteriologic, serologic, roentgenographic and histologic (liver, bone marrow and skin) evaluations were noncontributory. On July 22 the patient experienced respiratory distress and hypoxemia (Pa_{O_2} 40 Torr), and a chest film showed bilateral diffuse interstitial infiltrates. A transbronchial biopsy revealed *Pneumocystis carinii* pneumonia. This was complicated by a right-sided pneumothorax with the insertion of a chest tube. A 10-day course of intravenous trimethoprim/sulfamethoxazole therapy was given at a dose of 15 to 16 mg trimethoprim/kg/day. No granulocytopenia or thrombocytopenia was observed during or after treatment. Poor clinical response despite adequate serum sulfonamide concentrations led to open lung biopsy on August 6. A 21-day course of pentamidine, 4 mg/kg/day, was completed, with no evidence of nephrotoxicity during or after therapy. Because of the finding of severe interstitial fibrosis of the lung, in addition to persistent pneumocystis pneumonia, methyl-prednisolone was added to the pentamidine therapy on August 7. The patient continued to have infection of the tracheobronchial tree and pleural space due to *Pseudomonas aeruginosa*. In addition, a corneal ulcer with the same organism led to corneal opacity despite conjunctival treatment with amikacin and carbenicillin. *Candida albicans* fungemia was successfully treated with a 14-day course of amphotericin B (15 mg/day) and 5-fluorocytosine therapy. Bacteremia due to *Staphylococcus aureus*

From the Departments of Medicine (Drs Murthy, Smith and Baltch) and Pathology (Drs Parikh and Bishop), VA Medical Center, Albany Medical College, Albany, NY.

Address correspondence to Dr Smith, Assistant Chief, Infectious Disease Section, VA Medical Center, Albany, NY 12208.

TABLE I. Immunologic and Serologic Data

	Dates				
	July/81	Aug/81	Sept/81	Oct/81	Nov/81
Immunologic Data					
Serum immunoglobulins (normal range in mg/dL)					
IgG (620–1400)	1,200	—	1,090	—	—
IgA (60–350)	416	—	335	—	—
IgM (40–260)	229	—	108	—	—
Peripheral lymphocyte count cells/mm^3* (normal range 2.5–4 × 10^3)	410	467	472	—	—
Skin tests					
Tuberculin (5 TU)	Nonreactive		Nonreactive		
Mumps (0.1 cc)	Nonreactive		Nonreactive		
Candida (0.1 cc, 1:10,000)	Nonreactive		Nonreactive		
Lymphocyte studies					
OKT3 (T cells) (normal 53–80%)	—	27%	—	—	—
OKT4 (T helper) (30–56%)	—	6%	—	—	—
OKT8 (T suppressor) (15–32%)	—	27%	—	—	—
OKT4 : T8 ratio (0.9–3.5)	—	0.22	—	—	—
Phytohemagglutinin stimulation index					
Patient	—	—	—	1.61	—
Control	—	—	—	138.22	—
Serologic Data					
Cytomegalovirus (CF)†	<16	<16	—	—	—
Epstein-Barr virus‡					
IFA (viral capsid antigen)	1,600	3,200	800	—	—
Ox-cell hemolysin	<10	<10	10	—	—
Herpes-simplex virus	16	16	—	—	—
Toxoplasma gondii‡					
IFA	256	256	1,024	256	256
IFA-IgM	Neg	Neg	Neg	Neg	Neg

* Calculated by multiplying total leukocyte count by percentage of lymphocyte count in the differential count.

† CF denotes complement fixation titer.

‡ IFA denotes indirect fluorescent antibody. All serologic tests are reported in reciprocal titers.

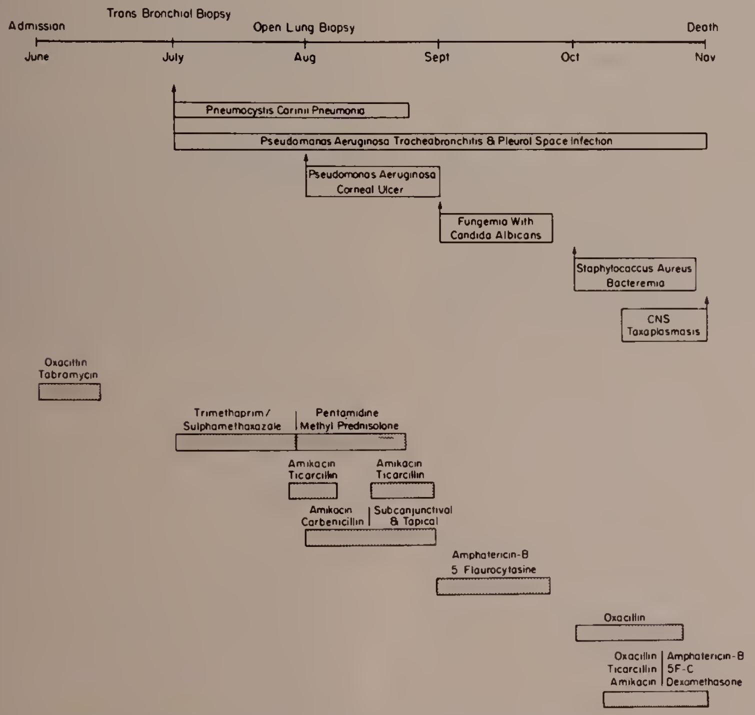

FIGURE 1. Infections and therapy during the clinical course of the patient.

was also successfully treated with oxacillin (10 days), and there was no clinical evidence of endocarditis at cessation of therapy on October 14.

On October 19, the patient had seizures, and obtundation developed. Because of a continued febrile course and multiple documented infections, meningitis was suspected. Cerebrospinal fluid examination showed no cells, normal glucose and protein, and negative cryptococcal antigen. Computerized axial tomography of the cranium demonstrated multiple areas of decreased radiodensity surrounded by bands of increased density after injection of contrast media. These findings suggested inflammatory lesions with associated edema (Fig 2). Because of the patient's critical state, multiple antimicrobial agents as well as dexamethasone for cerebral edema were given. Progressive mental deterioration, hypothermia, and hypotension followed, and the patient died on November 11, the 165th hospital day.

Immunologic and serologic data are shown in Table I. The patient had no cutaneous response to a variety of skin test antigens. He had marked, persistent lymphopenia with a depressed T-cell fraction. There was negligible T-cell mitogenic response to antigenic stimulation. The ratio of helper (OKT4) to suppressor (OKT8) T-cells was reduced. Serologic evidence suggested recent infection with Epstein-Barr virus, but not with herpes simplex virus or cytomegalovirus. There was no evidence for acute infection with *Toxoplasma gondii*.

An autopsy performed six hours after death revealed (1) severely fibrosed, collapsed lungs and no evidence of *Pneumocystis carinii* infection; (2) severe phlegmonous gastritis with intraperitoneal perforation of the stomach; (3) multiple foci of coagulation necrosis of both the grey and white matter of the brain with well-developed cysts and free trophozoites of *Toxoplasma gondii* (Fig 3). Cultures of lung, brain, liver, spleen, prostate, epididymis, and testis in cynmologous monkey kidney cells, human diploid embryonic lung cells, and one-day-old mice were negative for herpes simplex, cytomegalovirus, varicella zoster virus, adenovirus, enteroviruses, and myxo- and paramyxoviruses.

DISCUSSION

The patient described suffered a series of infections commonly associated with acquired defects of thymus-dependent (T-cell) lymphocyte function. The prolonged wasting illness and fever that preceded the onset of *P carinii* pneumonia is characteristic of AIDS. Although the etiology of this syndrome is unknown, the epidemiologic aspects suggest a transmissible agent[5] and a possible association with cytomegalovirus or Epstein-Barr virus, and human T-cell leukemia virus.[6,7] Transmission of AIDS appears to occur via blood or blood products delivered directly or by sexual contact.[5] This patient was a heterosexual male with a history of drug use of 15

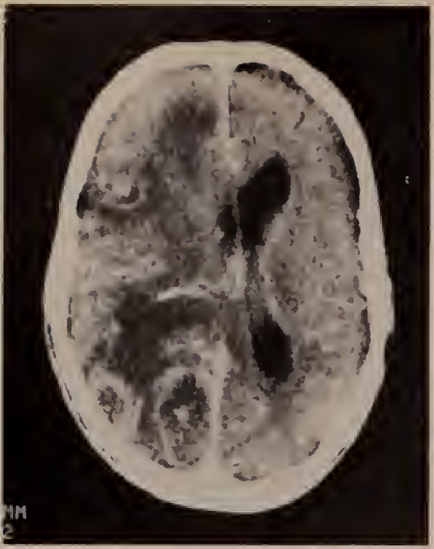

FIGURE 2. Computerized tomographic study of the cranium showing mass lesions and cerebral edema.

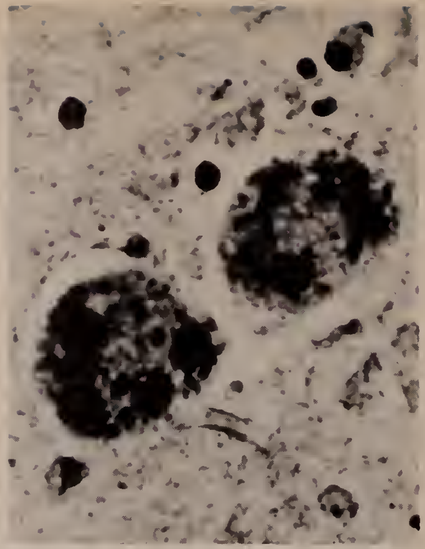

FIGURE 3. Microscopic section of brain indicating cyst forms of *Toxoplasma gondii.* (periodic acid-Schiff stain, original magnification ×900)

years' duration.

Of the five major infections that occurred during his 165 day hospital stay, two were caused by opportunistic pathogens—*P carinii* and *T gondii.* The use of trimethoprim/sulfamethoxazole failed to eradicate *P carinii* pneumonia. Although a three-week course of pentamidine appeared to eradicate this infection, complications with pulmonary fibrosis and pneumothorax resulting in a bronchopleural fistula caused inadequate oxygenation and need for a respirator throughout the patient's hospitalization.

Toxoplasmosis of the brain was the immediate cause of death. *T gondii* is an ubiquitous protozoan capable of surviving in multiple tissues and causing fulminant infections in immunocompromised, previously asymptomatic carriers.[8] Brain involvement is rare in toxoplasmosis in otherwise healthy adults, but congenital disease frequently involves the central nervous system.[9] Recently neurologic syndromes with diffuse encephalopathy, meningoencephalitis or cerebral "mass" lesions have been described in patients with neoplasia, collagen vascular diseases, and organ transplants.[8] Although most of these infections are thought to represent reactivation of dormant infections,[8] primary *T gondii* infections have been reported in patients with acute leukemia following granulocyte transfusions.[10] Cerebral infections with *T gondii* are described in patients with AIDS and seem to occur most frequently in Haitian immigrants. Of 30 patients with AIDS described in recent reports, encephalitis due to toxoplasmosis developed in 12.[11,12] Because of problems encountered in the serologic diagnosis of toxoplasmosis in this patient as well as in other patients with AIDS, biopsy for the presence of *T gondii* may be the only means of establishing this diagnosis. At autopsy this patient demonstrated cyst and trophozoite forms of *T gondii.* Restriction of this disease to the central nervous system with absence of dissemination to other organs, and presence of IgG but not IgM antibody to *T gondii* indicate reactivation rather than acute infection with this organism.

This patient is presented to emphasize the protean presentation of AIDS, the complex but possibly successful management of bacterial infections, and the need for tissue biopsy in establishing the diagnosis of opportunistic infections.

Acknowledgments. We wish to thank Dr V. D. Mottironi, NY State Department of Health, and Dr T. Spira, Centers for Disease Control, for lymphocyte function and virus isolation studies; Dr R. Deibel, NY State Department of Health, for virus isolation and serologic studies; and Mr Morris Gordon, NY State Department of Health, for serologic testing for *Toxoplasma gondii* and fungi. This study was supported by the Medical Research Service of the Veterans Administration.

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NYJ NEWS FEATURES

Drug treatment and nutrient therapy: the distinction blurs

> *. . . most clinicians date the third psychiatric revolution—the biochemical one—to the mid-1950s, when the potent antipsychotic tranquilizers and antidepressant compounds were synthesized and marketed. In truth, however, the third revolution in psychiatry began in 1949 with Cade's discovery of lithium for mania . . . Lithium's acceptance as a specific treatment and maintenance medication for manic depression marked the first time in the history of psychiatry that a simple, naturally occurring salt controlled a major mental disorder . . . Its acceptance could equal the impact of insulin or digitalis . . .*[1]

Without headlines or fanfare—indeed, almost unnoticed—an unprecedented interest in nutrition has seized medical investigators. A decade or two ago, the unorthodox nutritional research under way at American research centers would have been, at the least, startling. The notion that we are what we eat in certain fundamental ways—that the foods or supplements we ingest or eschew may actually spell the difference between optimal health and illness or impairment—was considered the ignorant preoccupation of "old wives" or the obsession of fanatics.

During the 1970s, a reputable medical voice or two, and ultimately a veritable chorus, began to echo a sentiment formerly confined to grandmothers and "nutrition-nut" fringe groups. In record numbers researchers began eyeing diet and nutrition more closely, subjecting the time-honored myths and legends to the methodologies of modern scientific inquiry, from scrupulous laboratory studies, conducted under controlled double-blind conditions, to epidemiologic scrutiny of personal eating habits among large populations.

By the early 1980s, most physicians were scarcely raising an eyebrow at the pronouncements that beta-carotene might prevent certain neoplasms (a hope dashed by subsequent studies); that alpha-tocopherol (vitamin E) might ease the travail of fibrocystic breast disease; that ascorbic acid (vitamin C) could reverse sperm agglutination (a report since called into question); and that a modest daily shot of spirits appeared to raise high-density lipoprotein cholesterol levels.

Not that medicine has totally ignored nutrition heretofore. The most overt consequences of malnutrition such as marasmus, kwashiorkor, and the cachexia of patients with cancer could hardly escape notice. The effects of specific vitamin deficiencies—scurvy, for example—have been known for generations. And, one can only imagine the elation following the discovery that many patients ostensibly suffering from severe mental illness were in fact ravaged by pellagra, reversible with adequate niacin intake.

But never before have the most subtle forms of inadequate nutrition received such intense attention. If much of the research on vitamins and trace elements has been disappointing or impossible to replicate, a different area of inquiry—the possibility that brain amine precursors, chiefly amino acids, may exert therapeutic effects on the brain and behavior—is just beginning to yield galvanizing, albeit controversial, findings. Some academicians remain hopeful that vitamins may prove to have clinical, especially psychoactive, value.

At the same time, laymen who may not necessarily know the rationale for the use of precursors such as L-tryptophan and L-tyrosine, let alone the investigational dosage schedules, are buying amino acid preparations at health food stores, a phenomenon that has some researchers worried and others incensed.

According to Victor Herbert, MD, professor of medicine at SUNY Downstate Medical Center, director of the division of hematology and nutrition at the Bronx VA Medical Center, and past president of the American Society of Clinical Nutrition, the precursor research is worthwhile, but "it has yet to be demonstrated in humans that supplements have any value" in the treatment or prophylaxis of any disease. In oncology especially, "no one responsible has reported any solid clinical findings," he says. Dr Herbert, author of several books on nutritional cultism and the health-foods "hustle" adds, "There are a lot of ripoffs going on."

Harold Lubin, MD, director of foods and nutrition at the American Medical Association, affirms that the use of nutritional supplements is still "very much in a theoretical state." He stresses, moreover, that a theory must be very well developed—as most nutritional hypotheses are not—before an ethical, large-scale clinical study can be performed.

Those who are formulating such theories pursue their work painstakingly. They are dismayed to see photocopies of their journal articles plastered on the walls of health food stores, which are under legal constraints not to orally promote supplements for any medical condition, and whose proprietors, in response to questions about dosage, reply, "Well, I can't give you that information, but my *customers* tell me. . . ."

FOOD FOR THOUGHT

Probably the best-known research on precursors is the neurologic work. Hope springs eternal that "brain food" may actually exist, and some of this hope seems justified by current discoveries.

At the Third Meeting of the International Study Group on the Treatment of Memory Disorders Associated with Aging, in Zurich, January 1984, psychiatrist Raymond Levy, MD, PhD, of London's Maudsley Hospital, reported significant or near-significant improvement in visuospatial and constructional capacities on psychometric testing and in self care among 24 subjects with Alzheimer's disease, who received high dosages of pure lecithin (maximum tolerable level, approximately 25 g/day) for six months, as opposed to a similar number of subjects given placebos.[2]

Plasma choline values were elevated in all of the subjects who received lecithin and, among those who demonstrated

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significant improvement, the values were double those in subjects who did not respond to the drug. But for unknown reasons, peak elevations occurred at one and four months. Moreover, other measures of lecithin-associated improvement were more impressive in the subjects who showed no improvement than in those who did improve. And, one psychometric measurement, verbal learning and memory, was unaffected by lecithin ingestion.

Richard J. Wurtman, MD, director of the Massachusetts Institute of Technology's Laboratory of Neuroendocrine Regulation, Cambridge, MA, who articulated the concept of "nutrients that act like drugs" in a seminal article on the subject in 1982,[3] noted that other presentations at the meeting, including a Hungarian study with cats and his own group's work with the rat caudate nucleus, support the clinical use of lecithin, whereas "the clinical evidence lags behind."

All such research is predicated on the cholinergic hypothesis of Alzheimer's disease; the theory states that this form of dementia arises from a defect in central cholinergic transmission, induced by unknown factors that cause a chronic imbalance between the endogenous synthesis of phosphatidylcholine (lecithin) and its breakdown into choline, for conversion into acetylcholine.

But Thomas Crook, PhD, chief of the Drug and Alcohol Program at the Center for Studies of the Mental Health of Aging, National Institute of Mental Health (NIMH), Rockville, MD, asserts that "there are now as many as 22 to 24 solid studies" of choline and lecithin administration, and "I think we have quite good evidence now that that doesn't work." He adds, "That doesn't mean the cholinergic hypothesis is wrong," pointing out, as does Dr Wurtman, that drugs that increase brain acetylcholine or inhibit the enzyme acetylcholinesterase that breaks it down have shown promise. He adds, "There's some evidence that lecithin could have additive beneficial effects with piracetam," and notes that there is even less evidence for the enhancement of physostigmine's effects by lecithin.

Dr Wurtman remains more optimistic that lecithin alone, or in combination with other drugs, will ultimately be shown to improve cognitive function or prevent further deterioration in dementia of the type evident in Alzheimer's disease. He points out that in Dr Levy's study, "one subset did seem to respond."

Recent research has focused on somatostatin neurons, which, like long-axon cholinergic neurons, sustain severe damage in Alzheimer's disease. Whereas various therapies have proved promising for ameliorating acetylcholine deficits, Dr Wurtman notes that replacing depleted brain peptides such as somatostatin is trickier because of the blood-brain barrier's impermeability to the exogenous, synthetic versions of such compounds.

John H. Growden, MD, an associate professor of neurology at Harvard Medical School, has studied the catecholamine and dopamine precursor L-tyrosine. He has shown that one third of 45 patients with early parkinsonism responded well to the supplement, with elevated dopamine metabolites measurable in their cerebrospinal fluid. This suggests that L-tyrosine might be an alternative to treatment with L-dopa, to which many patients eventually stop responding.

Finally, a preliminary but provocative Swiss study suggests that tyrosine may increase feelings of efficiency and vigor in persons aged 46 to 64.[4]

NUTRITION AND EMOTIONS

Working with Alan J. Gelenberg, MD, associate professor of psychiatry at Harvard Medical School, Dr Wurtman has reported improvement in a small series of patients with unipolar depression who were given L-tyrosine—along with pyridoxine (vitamin B_6), which is necessary for its metabolism, and sometimes with carbohydrate to induce insulin secretion, which lowers the peripheral levels of the other large neutral amino acids that compete for carrier-molecule transport to the brain. Dr Wurtman had previously shown in animals that tyrosine increases norepinephrine and dopamine synthesis—not indiscriminately, but under central nervous system regulation—only in frequently firing noradrenergic and dopaminergic neurons, respectively. Under an NIMH grant, the investigators are currently conducting a double-blind, placebo-controlled trial to compare the effects of tyrosine and imipramine in major depressive disorders.

Herman VanPraag, MD, chief of psychiatry at Albert Einstein College of Medicine, has given L-tyrosine, together with L-5-hydroxytryptophan, to eight patients with what was formerly known as endogenous depression, with therapeutic results. Previously Dr VanPragg had shown that the administration of L-5-hydroxytryptophan—an intermediate product in the conversion of L-tryptophan to serotonin—produces increases in cerebrospinal fluid concentrations of the major serotonin metabolite, 5-hydroxytryptamine (thought to be depleted in some patients with depression), suggesting that the precursor crosses the blood-brain barrier.

"In general, we have been interested in precursors besides those of serotonin," says Dr VanPraag, who has been exploring this area since 1958. "Dr Wurtman has done a lot of the preclinical

CREATING HEALTH NEEDS

What is the number one source of health information in the United States today? The obvious answer might be physicians, registered dieticians, nurses or health educators. Many people are shocked to learn that the major source is the mass media. Articles are published daily in local as well as national press by authors with little or no credentials extolling the virtues of a certain diet or a particular nutrient in large doses. This media blitz is reinforced by more than 2,000 books that promote herbal, vitamin, or nutritional remedies for treating or preventing nearly every disorder known to man. Annual sales of such books are about $65 million. The largest distributor of health related books and magazines is the Denver based Nutri-Books Corporation. A promotional piece entitled "Building your nutritional food business with books and magazines" sets the tone for their publications:

> . . . books are the 'cutting edge' of growth and directions of nutritional foods industry.
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> Books and magazine covers are designed like billboards. They reach out and 'grab' the customer. . . .
>
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> Sell a pound of wheat germ and it satisfies the customer's need. Sell a book and it creates a whole new set of needs in your customers.

For those patients who do not have time to read a book, there are numerous self-diagnostic tools available, among them the Herb Wheel. This device lists common ailments in general terms, and the user need merely spin the wheel to find the herb and spices for its treatment or prevention, or both. The Vita-Wheel lists the same information but proposes a cure with single or combination vitamin therapy, including minerals.

JOHN W. RICHARDS, Jr, MD
Department of Family Practice
Medical College of Georgia
Augusta, GA 30912

work in the field. His work and ours are very much related. We demonstrated that in man, you really can influence the synthesis" of biogenic amines. "Tyrosine and dopa are very controversial," he says, and there has been more of a consensus about the efficacy of 5-hydroxytryptophan in certain depressive illnesses than about that of L-tryptophan. In fact, Dr VanPragg notes, in Europe the former is considered sufficiently useful for treating depression that it is available by prescription in France and Germany. He adds that there is a biochemical basis for believing that the precursor increases brain catecholamine and indoleamine levels, and that a potentiating effect can be attained by giving it with tyrosine. "I think there is a future more in combining of precursors than in giving one alone," he says.

The precursor that has been given alone in the largest number of studies is L-tryptophan. There is little question in many quarters that the supplement, especially when taken with carbohydrate, has a soporific effect. To summarize just a few of the many investigations, L-tryptophan has been shown to increase drowsiness in healthy young men without causing performance decrements on sensorimotor tasks or exerting an anxiolytic effect.[5] It also decreases sensitivity to moderately painful stimuli[5] and, in some equivocal and much criticized research, appeared to ameliorate certain subtypes of depression.[6]

Other psychiatric studies of nutrient use have examined the possibility that various B vitamins, as well as amino acids, may have a palliative effect on specific syndromes. It has been suggested, for example, that pyridoxine could be helpful in depression associated with pregnancy and oral contraceptive use.[7]

Some psychiatric research centers apply nutritional approaches, in addition to pharmacologic ones. At Chicago's Rush-Presbyterian-St. Luke's Medical Center, for example, patients with affective disorders receive not only the standard medications, but also solo or adjunctive nutritional therapies including niacinamide, pyridoxine, L-tryptophan, L-tyrosine, and L-phenylalanine, as a precursor of the neuromodulator and endogenous amphetamine phenylethylamine (PEA). Use of the last amino acid was pioneered by Hector C. Sabelli, MD, PhD, director of the medical center's psychobiology laboratory, who has been studying PEA's possible role in determining affective responses for two decades. He has developed several controversial assays for the major PEA metabolite, phenylacetic acid (PAA), in urine and plasma, and has found that the majority of depressed patients have low PAA levels. With appropriate antidepressant therapy, these levels rise to those of control subjects, in parallel with normalization of the patient's affective state. Depending on the individual patient, the effective therapy may be a tricyclic or tetracylic agent, a monoamine oxidase (MAO) inhibitor, phenylalanine—given with pyridoxine, and sometimes with carbohydrate as well—or any other anti-depressant.

In contrast, Donald Klein, MD, professor of psychiatry at Columbia College of Physicians and Surgeons, New York, and director of research at the New York State Psychiatric Institute, does not use any nutritional supplements in his work. Dr Klein, coauthor of *Diagnosis and Drug Treatment of Psychiatric Disorders: Adults and Children*,[6] found in most psychopharmacologists' offices, originally reviewed the nutritional literature with an open mind; since then he has become disillusioned. He is perhaps most negative about an area of nutritional research not addressed in his book—the "orthomolecular" school of thought. Originally stressing megadoses of B vitamins for treating schizophrenia, an approach popularized in books such as Mark Vonnegut's autobiographical account of his psychosis,[8] orthomolecular treatment has spread to encompass conditions such as Down's syndrome. Henry Turkel, MD, a private physician in Southfield, MI, reports successful treatment of both the latter disorder and mucopolysaccharide storage diseases through use of what he calls the "U-series," a combination of 60 nutrients and drugs that range from calcium pantothenate and riboflavin to thyroglobulin and dental anesthetics.

Commenting on the pursuits of orthomolecular practitioners, Dr Klein remarks that when anyone claims a given regimen works, "it's his scientific obligation to document its effectiveness. They haven't." Most neuroscientists agree. His skepticism encompasses even the more reputable scientific studies—those of the proponents of precursor therapy, for example.

Having initially examined the proposition that L-tryptophan could potentiate the effect of MAO inhibitors, he says, "Again, there was originally a flurry of articles, but nothing since," adding that he tried it in his own practice without success. He notes that there is little or no evidence that pyridoxine can ameliorate the side effects of these agents.

In summary, Dr Klein says, "We wish this [nutritional] stuff would work, [but] the field is riddled by faddism." If the nutritional approach had merit, "we would have seen some hard evidence by now."

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Dr VanPraag comments, "I must say I disagree. There are certain reasons why some find [biogenic amine precursors] effective and others do not—differences in dosages and blood levels, for example." The number of studies in the area is small, he acknowledges, and "the final conclusion is not yet passed."

Dr Wurtman concurs, and referring to the lecithin studies, he points out that pure lecithin has been available only for about 18 months. He adds that L-dopa was not recognized as an effective treatment for Parkinson's disease until the late 1960s; throughout the early part of the decade, he reminisces, it was dismissed, if not derided outright. Regarding the recent plethora of precursor strategies, he says, "I would give them another five or six years."

Obesity and Other Ills

Dr Wurtman's wife, Judith Wurtman, PhD, a cell biologist and nutritionist at MIT, studies the plight of the overweight who are relentlessly driven to snacking, especially on sweet and starchy foods. In one study she has administered the serotonin substitute fenfluramine to 45 such subjects, reducing their carbohydrate craving significantly.

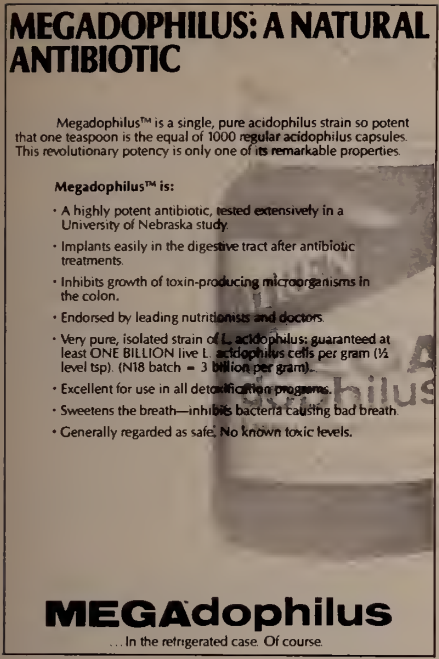
She notes that the appetite suppressant has no effect on eating behavior at meals. The subjects' dietary downfall is their irresistible craving for between-meal carbohydrates, and this is what the drug diminishes. There is preliminary evidence that L-tryptophan may have a similar effect on some subjects' snacking behavior.[9]

Dr Wurtman has also initiated or completed studies aimed at elucidating what she posits as a physiologic need for tryptophan to increase brain serotonin levels in the obese. One current aim, she says, is to recruit non-carbohydrate-loving snackers, to see how they might differ. "We're rewriting the ads [to attract volunteer subjects] to get people who snack on cheese and cold cuts," she elaborates, an attempt that has so far netted only about 10 subjects. She would also like to study those who simply do not snack, to test her hypothesis that weight reduction through behavior modification—taking smaller portions at meals—is relatively easy for such subjects.

But, for the great majority of the overweight, it seems that serotonin deficits virtually guarantee failure on traditional weight-loss regimens.

"It's clear that the insulin response is less effective in many overweight people," comments Dr Wurtman; thus they may need more dietary carbohydrate to lower the levels of large neutral amino acids other than tryptophan, so that a sufficient level of tryptophan reaches central nervous system binding sites. The dietary solution for these people, she believes, is to take regular carbohydrate snacks, but with little fat: jelly beans, for example, as opposed to rich cakes and cookies.[10]

In contrast, Adam Drewnowski, PhD, at that time an assistant professor at the Laboratory of Human Behavior and Metabolism of Rockefeller University, New York, and M. R. C. Greenwood, PhD, professor of biology at Vassar College, Poughkeepsie, reported at the 1983 meeting of the Federation of So-



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cieties for Experimental Biology (FASEB) that people who claim to disdain fat actually like various milks and creams increasingly as the drinks are sweetened with generous quantities of sucrose. They later found that normal-weight subjects reject fat at a certain point, regardless of sugar content, whereas the obese keep going, as do the formerly obese—suggesting that overweight people's legendary love of carbohydrates is actually a passion for carbohydrate-rich fats. At this year's FASEB meeting, they reported that patients with anorexia nervosa show the "carbohydrate phobia" previously attributed to them only in relation to sweetened fats, as well as a dislike for unsweetened fats.

Asked to comment, Dr Wurtman noted that these investigators used a sip-and-spit technique, in which the subjects never actually swallowed the foods in question; therefore they were dealing with hedonic preference for the taste of carbohydrate and fat, rather than with the physiologic craving or need for the latter that seems to characterize the majority of her research subjects.

In joint research with colleagues including Erik Heraief, MD, chief of medicine at University Hospital in Lausanne, Switzerland, Dr Wurtman found that consumption of the "protein-sparing modified fast," often recommended for obese patients, substantially lowered the ratio of plasma tryptophan to other large neutral amino acids in obese and control subjects alike.[11] Administration of up to 2 grams of L-tryptophan failed to change this ratio to that observed when high-carbohydrate, low-protein diets are consumed. (The amino acid is ineffective in promoting serotonin synthesis when its ingestion accompanies a high-protein intake.) Moreover, even baseline plasma tryptophan levels were lower, and those of the other amino acids higher, among the obese subjects.

This study was undertaken, Dr Wurtman adds, because one of her co-investigators, P. Burckhardt, MD, was obtaining such poor results when he attempted to help obese patients by prescribing the classical low-carbohydrate, high-protein diet.

For the vast majority of overweight people who are not taking drugs but rely on frequent snacks, Dr Wurtman's message is clear: Overeating represents a very real physiologic need of the obese for enough dietary carbohydrate to produce adequate brain serotonin levels.

Interestingly, psychiatrists seem quite aware of this phenomenon, she says, judging from their response to her research findings; other physicians may not be.

Women of normal weight are known to crave carbohydrates before their periods. From a recent survey encompassing 600 respondents, Dr Wurtman learned that for two to seven days, 93% of the women reported craving sweets; 87% starches; 87% sweet, fatty foods; and 39% protein. "I'm sure it has to do with serotonin," she says.

For premenstrual syndrome (PMS), there is little new nutritional help on the horizon. Cynthia Cooke, MD, co-author of *The Ms. Guide to a Woman's Health*[12] and associate clinical professor of obstetrics and gynecology at the University of Pennsylvania School of Medicine in Philadelphia, notes that pyridoxine, in dosages of 50 to 100 mg, is still regarded by some as helpful for premenstrual edema.

As for the latest fad promulgated by health-food-store leaflets, a purported PMS panacea dubbed "evening primrose oil," Dr Cooke says, "I don't know what it is, or the therapeutic rationale for it. But there have been several reports of poisoning in the literature."

PICK YOUR POISON

Concern about toxicity is not limited to nostrums touted by practitioners, or hucksters, outside the confines of organized medicine. Indeed, for all the doubt surrounding the efficacy of nutritional medicines, worry about the potential threat to health that supplements may pose is equally intense.

Allen L. Forbes, MD, associate director for nutrition and food sciences at the Food and Drug Administration's (FDA) Bureau of Foods, Washington, DC, says that any efforts the agency might make to regulate the sale of nutritional supplements were killed by the Proxmire Amendment, which, in effect, put the onus on the FDA to prove that a given substance is harmful.

Lacking the funds to research supplements on a large scale, Dr Forbes continues, the agency is largely reliant on studies such as the investigation of pyridoxine-associated neurotoxicity.[13] Daniel Rudman, MD and Patricia Jo Williams of Emory University School of Medicine, Atlanta, noted that a contaminant, rather than the nutrient itself, could have been to blame, as the 2% ceiling imposed on impurities by the FDA becomes a high ceiling indeed at dosages exceeding 2,500 times the recommended dietary allowance.[14] Others have cited the potential problems of contaminants, noting, for instance, the recent discovery of lead contamination in some calcium supplements.

"In essence," Dr. Forbes points out, "the Proxmire Amendment says that potency can only be governed on the basis of hazard, not on that of sound nutritional practice." At the same time, he comments, never before in history have humans taken such high dosages of such record numbers of nutrients. The FDA recently conducted a soon-to-be-published telephone survey indicating that 40% of the nation's residents con-

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sume nutritional supplements. (Included in this statistic are those who take a daily multiple vitamin tablet.)

The toxicity of particular nutrients is becoming increasingly clear, says Dr Forbes. "We're concerned about every nutrient required by man. There are no safe minerals." Zinc impairs the body's immunologic response, he says, and one manufacturer recently produced a tablet containing a lethal dose of selenium.

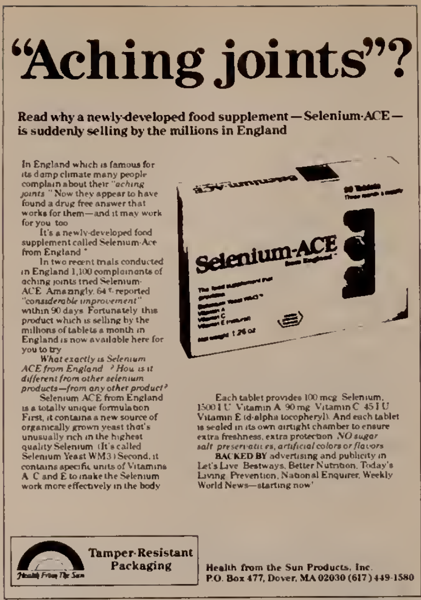
As for problems with brain amine precursors, Dr Forbes suggests that by the time researchers' therapeutic results reach the lay press, dosages may have been inflated, conceivably leading to the ingestion of neurotoxic amounts.

The problem is that the absolute toxic levels of many nutritional supplements are simply unknown, and ethical concerns preclude human studies. "One wonders whether there [will] be epidemics," Dr Forbes reflects, or simply subclinical, perhaps undetected, toxicity. "But I can virtually guarantee you, we will learn that there are bad effects from excess intake of nutrients," he prophesies. "No one ever thought in his wildest dreams that anyone would take 3 grams of B_6 a day. No one has taken thiamine that way—what on earth for?"

He adds that labeling is limited by law. Thus a bottle of L-trytophan tablets, for example, can bear a vague statement such as "Take one or more tablets daily or as directed." If a producer made the claim that the amino acid was helpful for sleep disorders, "we'd seize it," he says. In Dr Forbes's opinion, the supplement "clearly causes sedation at high dosages," and one must differentiate its probable use by nonpatient, health-food store patrons from its therapeutic use for patients with depleted bioamines.

Given the constraints on FDA regulation of supplements, he says, "We have to wait for people to start poisoning themselves on the sidewalk."

Others are perhaps a bit more sanguine. During Poison Control Week in March, Rush-Presbyterian-St. Luke's Medical Center elicited a spate of inquiries to its Poison Control Center when it alerted the public to the problem of child poisonings. Hundreds of Chicago-area children suffer each year from overdoses of vitamins—usually the sweet, chewable variety—the medical center reported. According to Poison Control Center supervisor Jack Lipscomb, RPh, although children can die from the iron they ingest in these multivitamins, "generally we don't see a major problem with health food products." A consultant to the Rocky Mountain Poison and Drug Center in Denver agrees that toxicity from vitamins and other health food supplements, ingested chronically and in megadoses, is a relatively rare problem.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The first case of poisoning from selenium supplements was documented in 1984 by the Centers for Disease Control. A 57-year-old Long Island woman experienced loss of hair and fingernails, nausea and vomiting, and fatigue after ingesting megadoses of selenium for two and a half months. The woman obtained the mineral supplement from a health food store because she had been led to believe that it would prevent cancer and heart disease. The Food and Drug Administration is investigating the manufacturer of the supplement; the tablets contained 182 times the amount of selenium stated on the label.

MMWR 1984; 33:157–158

What about the potential toxicity of physician-monitored therapeutic doses of amine precursors? Most researchers feel comfortable with the dosages they have established. Dr Richard Wurtman notes that side effects from choline, lecithin, and L-tyrosine are minimal, probably because cholinergic and catecholaminergic neurons use the precursors selectively. Serotonergic neurons, however, have no "choice" in responding to tryptophan, and this supplement can cause nausea, vomiting, headache, and undesirable drowsiness at relatively high dosages.

As for the issue of such supplements' clinical efficacy, Dr Robert Prien, chief of the Affective Disorders Unit, NIMH, takes something of a wait-and-see attitude. "The studies that have looked at L-tryptophan have not been overly productive," he asserts. The level of success achieved with L-tyrosine and 5-hydroxytryptophan remains to be seen. Moreover, unlike Dr Van Praag, who regards the newer precursors as potentially attractive to drug firms—as L-dopa proved to be—Dr Prien proposes that these supplements "don't have much in the way of commercial interest." Dr Prien concludes, "I don't think the data warrant a great deal of enthusiasm. They warrant hope."

Elizabeth Rasche González

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Ms Gonzalez is a medical and science writer in Chicago.

PREVENTING REACTIVE HYPOGLYCEMIA: THE GREAT MEDICAL DILEMMA

By Fred D. Hofeldt, MD, 135 pp. St Louis, MO, Warren H. Green, 1983. $18.50 (hardcover).

The subtitle of this book, "The Great Medical Dilemma," reflects the author's involvement in clinical research to define specifically the syndrome of "reactive hypoglycemia" and to separate it from the confusion promulgated in the popular press and in some medical circles. In this small volume he summarizes the history, physiology and differential diagnosis of reactive hypoglycemia, as well as the specific criteria involved in diagnosing the condition. Although he refers to his work as a textbook, it is not a complete reference work. In a well-organized and accurate but discursive, "homey" fashion, he reviews the polemics among clinicians who have applied the name hypoglycemia to a variety of medical conditions and narrows the diagnostic criteria. In only two of 10 patients previously diagnosed as having reactive hypoglycemia was the diagnosis confirmed by his strict criteria.

A proper perspective of the problem is given in a chapter concerning the differential diagnosis of all clinical entities that present with low blood sugar. A classification system that divides those cases in which symptoms are manifested after fasting from those that appear after glucose consumption helps to define the reactive type of hypoglycemia. Another chapter presents an excellent differential diagnosis of "spells," since many of the patients with hypoglycemia have evidence of cerebral neuroglycopenia.

The author emphasizes the fallacies inherent in using the glucose tolerance test for the diagnosis of reactive hypoglycemia. Since one quarter of the population has low blood sugar (below 50 mg %) at the end of the test without manifesting any symptoms, the author has developed the classification of "transitional low blood glucose state." These patients do not have reactive hypoglycemia.

This transitional state can be characterized as alimentary, diabetic, hormonal or idiopathic. Each category is well discussed with examples of blood insulin secretion, blood cortisol and growth hormone levels, and urinary catecholamine excretion at the nadir of blood sugar levels.

The author's clinical background led him to include a chapter with a simple and practical assessment of hypoglycemic disorders. He emphasizes the need for a clear-cut history showing that the patient's symptoms (including "spells") are postprandially-related and that the patient has been a food abuser—namely eating excess amounts of refined carbohydrates. The subsequent beneficial response to an isocaloric diet without refined carbohydrates, given in three to six feedings, that leads to the abeyance of symptoms is a good diagnostic marker. Elaborate tests are not needed. In psychosomatic cases, an estimation of the insulin response to the oral glucose test and an estimation of the blood cortisol and growth hormone response at the nadir of the blood sugar level can rule out hypoglycemia as a cause. In alimentary cases and patients with diabetes and reactive hypoglycemia, the insulin response test can demonstrate hyperinsulinemic or delayed insulin responses.

The author is philosophic and forward-looking in the last chapters. With the identification of "idiopathic reactive hypoglycemia" as a clinical entity, the exact cause of its symptoms needs more clarification. It was coincidental that when I received this book for review on February 3, 1984, I simultaneously received *JAMA* (vol 251, no 5). On page 612 is an article entitled "The use of plasma epinephrine responses in the diagnosis of idiopathic postprandial syndrome." Most of the findings described in the book are confirmed, and the syndrome is well established although with a different name. Measurement of the epinephrine and norepinephrine content of the blood during a glucose tolerance test with continuous blood sugar monitoring proved that the catecholamines do rise, but the patients had symptoms 10 to 20 minutes before the catecholamines were significantly elevated. The authors believe that the enhanced release may be a consequence of a sensitive brain to relative central nervous system neuroglycopenia at the glucose nadir rather than the cause of clinical manifestations.

This book is a clear exposition of a medical condition that is not uncommon and is easily amenable to treatment, although the physiology is not yet clearly defined. It is easily readable and is recommended for physicians who encounter the postprandial syndrome seen in the many "food abuser" patients.

MILTON B. HANDELSMAN, MD
Long Island College Hospital
New York City 11201

CONTROVERSIAL NUTRITION POLICY ISSUES

Edited by Giorgia R. Solimano, MD and Sally A. Lederman, PhD. 429 pp. Springfield, IL, Charles C Thomas, 1983. $34.75 (hardcover)

This book is a series of essays written by graduate students enrolled in the course "Public Health Nutrition" at the Columbia University School of Public Health and Institute of Human Nutrition. The students analyze nutritional problems in relation to cultural, political, economic and social factors, and they develop appropriate policies for the elimination of these problems. The editors are a physician and nutritionist with experience in maternal and infant nutrition. The book addresses issues in public health nutrition, most of which are relevant to preventive medicine, health promotion and disease prevention and would be of interest to the primary care physician and his or her patients.

The articles are divided into three sections. Food, Nutrition and Development explores such issues as cash cropping, the green revolution in Brazil and India, malnutrition in developing countries, China's approach to nutrition, food aid to Chile, drought bordering the Sahara desert, and changes in the diet of South Africans. In Regulatory Problems in Food and Nutrition, topics such as saccharin, PCBs in nursing infants, United States dietary goals and Recommended Dietary Allowance for pyridoxine are discussed. Nutrition and Disease considers coronary heart disease, vitamin C, "bottle babies," supplementation in pregnancy, iron and infection, "benign" parasitoses, and alcohol consumption by the American Indians.

The articles are generally well written and interesting, although a bit polemical. Overall, there is considerable factual, referenced information on controversial nutrition policy issues that is not readily available to physicians. The authors attempt a balanced presentation. They recommend solutions to the problems, offering sugestions that are sometimes provocative and in all cases thoughtful. Particularly enjoyable are the discussions of the dietary goals, the lipid hypothesis and the role of vitamin C in maintaining health. The review of pyridoxine is less impressive.

The book is a photo-offset from a typed manuscript but is easily read. There are minimal illustrations and an appropriate number of tables. The articles average 20 pages in length.

The authors' analytic approach to public health and nutrition escapes being pedantic; it is refreshingly original and should be encouraged. The editors and authors are to be congratulated for a worthy endeavor that is both readable and informative.

ELAINE B. FELDMAN, MD
Medical College of Georgia
Augusta, GA 30912

THE CROHN'S DISEASE AND ULCERATIVE COLITIS FACT BOOK

Edited by Peter A. Banks, MD, Daniel H. Present, MD, and Penny Steiner, MPH. 194 pp. New York, Charles Scribner's Sons, 1983. $14.95 (hardcover)

The purpose of this book is to provide a comprehensive and readable description of inflammatory bowel disease (IBD) for patients and their families. The editors have succeeded in this effort. It is not easy for a physician to evaluate such a book from the viewpoint of a layman, but I found the writing to be suitably lacking in jargon. There is a certain amount of repetition, but this is probably useful for the intended reader.

The text is divided into three main sections: clinical information, therapy, and a section called "Living with the Diseases." The last includes a number of topics that should be helpful to patients with IBD. These include coping with hospitalization, obtaining insurance and dealing with disability. These illustrate the practical value of the book.

The presentation of all of the sections is excellent. The chapter on nutrition provides guidance and rather complete coverage of a topic that is important and often appreciated more by the patient than by the average physician. This applies to the chapter on emotions as well. The importance of the stress of chronic illness on the patient and on family members is emphasized. The role of family therapy is also discussed.

There is a certain uneven quality to some of the chapters, particularly in emphasis. This probably represents the interests and biases of the contributing authors. For example, the discussion of immunology and T-cell subsets may be too sophisticated; there is more information about immunosuppressive therapy than about sulfasalazine or corticosteroids. The section on cancer acknowledges that statistics on cancer risk in colitis may not represent the actual risk for all long-term patients but still quotes risk figures of 20% to 30%. Patients with colitis may have difficulty in evaluating this.

These comments aside, I would highly recommend this book for patients with IBD. In fact, I found it very useful myself and recommend it for physicians. The most impressive aspect of this book is the level of sophistication of the material. This is a tribute to the lay members of the National Foundation for Ileitis and Colitis who have long championed the concept of the well-informed patient. This book represents a culmination of their efforts in advancing research and education in IBD and might stand as a model for patients with other diseases.

CHARLES D. GERSON, MD
Mount Sinai Medical Center
New York City 10029

WORKERS AT RISK

By Dorothy Nelkin and Michael S. Brown. 220 pp. Chicago, The University of Chicago Press, 1984. $20.00 (hardcover)

"I work in the kidney dialysis unit. . . . On Thursdays, after everybody leaves, I sterilize with formaldehyde. That's the Biggie. I put four gallons of formaldehyde, 37 percent concentration, in the MAX supply tank . . . . there are 31 canisters in this room . . . . I fill each of those with formaldehyde and turn on the recirculating pump. . . . There's no tops on the containers, so it gets in your eyes and respiratory system . . . . but I like the job. It's necessary to someone because our patients can't live without it." Jill is a dialysis technician quoted in *Workers at Risk*.

In a format similar to that utilized by Studs Terkel in *Working*, Nelkin and Brown in *Workers at Risk* interviewed workers exposed to various types of chemicals about their perceptions of and concerns about the occupational risks they face daily. Nelkin has previously written on public policy issues in science and technology and is a professor in the Department of Sociology and in the program on Science, Technology and Society at Cornell University. Brown is a PhD candidate in the latter.

The title of this book is a bit misleading since the book addresses attitudes, fears and anxieties of workers with respect to only chemical hazards at the worksite.

Each chapter starts with a factual description of the workers' comments as well as current information pertaining to their concerns. The final chapter summarizes the feelings and perceptions of workers. In the appendices, information about each worker, the types of chemicals they are exposed to and possible health effects associated with these chemicals are presented. In addition, an annotated bibliography by chapter topic is included.

The general impression one gets from reading this book is that the majority of employees are blue-collar workers who are exposed to various amounts and forms of toxic substances on a daily basis. The universal battle between management and worker prevails, especially with regard to occupational health. No solutions are offered as to how to remedy this problem. However, discussions about current laws such as the right-to-know law are presented along with the limitations of such recourse. It must be noted that only the workers' experiences were included in the text.

An interesting fact brought out by the authors was that if workers cannot obtain health and safety information from their employers, they can contact the manufacturers of the chemicals that they are exposed to for this information. Manufacturers generally comply. After reading *Workers at Risk*, one begins to wonder if these manufacturers are the same ones cited for not addressing the health and safety issues of their own employees.

Workers at Risk is a solid complement to any course in occupational health. It was not meant to be a textbook and therefore is able to supply information about the actual concerns of the workers exposed to chemicals on a daily basis.

BETSY KAGEY, MSPH
Glens Falls, NY 12801

COMPUTERIZING YOUR MEDICAL OFFICE: A GUIDE FOR PHYSICIANS AND THEIR STAFFS

By Dot Sellars, 228 pp, illustrated. Oradell, NJ, Medical Economics Books, 1983. $17.50 (softcover).

Physicians have shown resistance to the use of digital computers in private practice. This attitude may be due to a general lack of computer literacy and the dehumanizing stigma that was frequently associated with computer technology in the past. The more widespread availability of computers, coupled with the increasing complexities involved in clinical practice, is making the use of computers in the private practitioner's office more commonplace. Rapid advances in computer technology are leading to the availability of more powerful machines at relatively low prices. This should further accelerate the use of computers by the private practitioner.

Ms Sellars has written a book that focuses on computers and computer applications related to the business aspects of medical practice. This indeed seems to be a good way to introduce physicians to the versatility of modern digital computers. Topics are presented in such a manner as to minimize the use of computer jargon and the more technical aspects of computers. The author draws from her day to day experiences in the design and implementation of computer systems in the medical environment. The chapters address such topics as the advantages and cost effectiveness of computers, selection of the proper hardware and software, and the multiplicity of functions of the computer.

Unfortunately, the author limits her discussion to the use of mini-computers. This then limits discussion to sophisticated and expensive systems suitable for large or group practices. Costs of such systems usually range upwards of $50,000. With rapidly advancing technology, powerful micro or desk-top computers, at costs of less than $10,000, are finding extensive application. Since there is no discussion of micro-computers, the reader is given no measuring stick against which to judge which type of computer will best meet individual needs. Although it is true that at present a micro or desk-top computer cannot handle all of the applications presented, they can still handle many of them and at substantially lower costs. It is also true that physicians with small or medium-size practices might decide that applications available with a micro-computer will suit their needs.

To appreciate fully the information presented in this book, the reader should have some knowledge of fundamental computer concepts. Without this knowledge some of the richness of the author's experience will be lost to the average physician.

Ms Sellars' book contains a wealth of information pertaining to the proper organization of the various components involved in computerizing business aspects of private practice. She exposes many of the pitfalls and often-overlooked aspects involved in designing an efficient system. In this regard the book is useful for all physicians, but it is written for the physician with a large or group practice and some knowledge of computer fundamentals.

JAY FLEISHER, MS
State University of New York
Downstate Medical Center
New York City 11203

BIOMEDICAL INSTITUTIONS, BIOMEDICAL FUNDING, AND PUBLIC POLICY

Edited by H. Hugh Gudenberg, MD, 212 pp. New York, Plenum Press, 1983. $29.50 (hardcover).

This book is the second of several intended to inform both the biomedical community and interested laymen of the political and economic implications of biomedical research. This volume focuses on the role of foundations, similarities and differences among research establishments, the costs of research and economic "fallout," and an update on "dollar savings."

The book is a collection of 11 essays and articles—at least four of which have appeared elsewhere in print—written in some cases by well-known figures. Several chapters have significance for scientists, including "Basic Biomedical Research: A Cost-Benefit Analysis," "Molecular Biology: Application to Prenatal Diagnosis of Genetic Disorders of Hemoglobin," "Histocompatibility Workshops: Economic Impact," and "World Endemic Disease: Costs and Potential Fiscal Benefits of Medical Research." Laymen might be interested in "Economics of Health Care," "Foundations and their Contributions to the Shaping of Health Policy," and "Differing Approaches to Biomedical Research: The NIH, The Academic Medical Center, and the Pharmaceutical Industry."

Despite the title, the primary purpose of the book is, according to the editor, "for the scientific community to prove to Congress that federal funding of basic biomedical research results not 'merely' in lives saved but in dollars saved." A collection of essays is very difficult to integrate into a common theme, and this collection is no exception. The chapters on foundations and the economics of health care appear to have no relationship to the other chapters or even to biomedical research.

Governmental budgeting involves compromises of political and other values. The scientific community has been trying in vain since World War II to develop an "economic savings" argument for biomedical research and development that would immunize this field from the political battle. But the book ignores the historical aspect, and it makes no better a case than the propositions of past years. In fact, biomedical research cannot and should not be immunized from the political battle any more than other endeavors to create a "good society."

Interestingly, one article points out that "ordinary cost-benefit analysis procedures are inadequate to account for the advances in health science and technology that are attributable to the efforts of biomedical research." Congress has long since accepted the general proposition of the economic costs of illness. But the book at no time takes into account that in health and medicine new discoveries and new technologies have led to higher costs, not to savings. Because of the value placed on human life, the proportion of the gross national product (GNP) devoted to the health industry has risen from 3% to over 10% during the past 50 years. Much of that increase came about from discoveries through research and consequent development. In the chapter on economics, the author points out that the focus should be on how much better an innovation is, not how good it is. How do the expected benefits—not necessarily fiscal—compare with others derived by spending money in alternative ways?

It would be useful to have a book address public policy for biomedical research in other than fiscal terms. Many questions come to mind. How are research priorities established beyond the initial question of "good science" which the NIH study sections address? What is the proper balance between basic and clinical research? How do we transfer new knowledge into technology, and what are the right means and organizations to assess those transfers? What has been the impact on medical education and patient care of making our medical schools the center of biomedical research? In times of economic restraint why should industry not fund a substantial amount of basic research, as is the case in the communications and electronics industries?

Some scientists may gain satisfaction from the limited fiscal approach to public policy presented in the book. But the intelligent layman may not understand many of the articles and will find those that he does understand—on foundations, economics of health care, and excellence and creativity—hardly relevant to his broad concern for the non-fiscal issues of public policy involving biomedical research.

IRVING J. LEWIS, MA
Albert Einstein College of Medicine
of Yeshiva University
New York, NY 10461

HOW TO SURVIVE MEDICAL SCHOOL

By Toni Martin, MD. 180 pp. New York, Holt, Rinehart, and Winston, 1983. $13.95.

This book, written by an internist who recently completed her medical education, is by no means a unique contribution to the medical literature. For decades, physicians have written autobiographical accounts of their unique educational experiences. However, while books of this genre, such as *Gentle Vengeance* and *The Making of a Surgeon*, have focused upon one specific period, this book describes the entire process. Its title is deceptive, as the author includes experiences extending from her premedical through her post-graduate education, and all of this in less than 200 pages.

The other major fault in this book is its subjectivity. The survival of medical school, like the field itself, is an art and not a science. The author does not hold this belief. She claims that "all medical students are depressed" and advocates attending class and not confiding in the dean of students as survival strategies. However, as a medical student I was not depressed and achieved optimum success by not attending class and by confiding in the dean of students. Advice presented in this manner can be of little benefit to the future medical student.

Many of the author's discussions, such as the exclusive pursuit by physicians of goal-oriented activities, emphasis on test scores and not bedside manner, and hypocritical advice given to patients in regard to rest, exercise and work, are insightful but are far too brief.

Her cynicism is frequently blunt and amusing. She comments on the application process for post-graduate training: "You could explain to interviewers why you wanted to go to medical school, but no one in his right mind actually wants to be an intern." However, it often becomes extreme as in her criticism of physicians in other specialties and her description of the county hospital as the "cesspool of humanity."

If additional editions are written, several modifications are necessary. Limitations should be made on the span of both time periods and topics. The author should concentrate on specific issues that affected her training, namely those of being a black woman in a profession dominated by white men. These are mentioned, but not in detail. Lastly, the index, which indicates the author's attempt at creating a reference text, should be eliminated.

Unlike recent books such as *A Survival Manual for Medical Students* and *Coping in Medical School*, this book offers no general techniques for handling the various stresses of medical education. Largely anecdotal, it should be retitled *How I Survived Medical School*, and in its present form, this book cannot be recommended.

RICHARD A. BENEDIKT
McLean Hospital
Belmont, MA 02178

In addition to these listings, the Journal *will publish obituaries written by physician readers. Inquiries should first be made to the Editor.*

Robert Saul Aaron, MD, Great Neck. Died April 1, 1984; age 60. He was a 1946 alumnus of the State University of New York Downstate Medical Center. Dr Aaron was a Fellow of the American College of Cardiology, a Fellow of the American College of Physicians, and a Diplomate of the American Board of Internal Medicine. He was a member of the Academy of Medicine, the American Public Health Association, the Nassau County Medical Society and the Medical Society of the State of New York.

Cecil Abraham, MD, Mamaroneck. Died October 17, 1983; age 78. He was a 1929 alumnus of the University of London Faculty of Medicine, London. Dr Abraham was a Diplomate of the American Board of Pediatrics. His memberships included the American Academy of Pediatrics, The New York County Medical Society and the Medical Society of the State of New York.

Ernest Alexander, MD, Jackson Heights. Died March 27, 1984; age 74. He was a 1934 graduate of the Deutsche Universität Medizinische Fakultät, Prague. Dr Alexander was a member of the Medical Society of the County of Queens and the Medical Society of the State of New York.

Elmer E. Amerman, MD, Jackson Heights. Died May 14, 1984; age 85. He was a 1921 graduate of New York University College of Medicine. He was a member of the Medical Society of the County of Queens and the Medical Society of the State of New York.

Sidney F. Auerbach, MD, Brooklyn. Died March 2, 1984; age 75. Dr Auerbach was a 1936 graduate of the Licentiate of the Royal College of Physicians of Edinburgh. He was a Qualified Fellow of the International College of Surgeons and a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Morris H. Bernstein, MD, New York. Died March 7, 1984; age 61. He was a 1946 alumnus of the Vanderbilt University School of Medicine. Dr Bernstein was a Diplomate of the American Board of Psychiatry and Neurology. He was a member of the Academy of Medicine, the American Psychiatric Association, the American Psychoanalytic Association, the New York County Medical Society and the Medical Society of the State of New York.

Lester Joseph Candela, MD, Great Neck. Died April 18, 1984; age 75. Dr Candela was a 1942 graduate of Marquette University School of Medicine. His memberships included the Academy of Medicine, the New York State Surgical Society, the American Society of Abdominal Surgeons, the Medical Society of the County of Queens and the Medical Society of the State of New York.

Milton Cantor, MD, Brooklyn. Died March 19, 1984; age 74. He was a 1937 graduate of Karl-Franzens-Universität-Medizinische Fakultät, Graz. Dr Cantor was a Fellow of the American Academy of Family Physicians and a Diplomate of the American Board of Family Practice. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Mortimer Jacob Cantor, MD, Miami, Florida. Died July 14, 1983; age 86. He was a 1921 graduate of New York University College of Medicine. Dr Cantor was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Fred Cohen, MD, Brooklyn. Died January 28, 1984; age 80. He was a 1930 alumnus of New York Medical College, Flower and Fifth Avenue Hospitals. Dr Cohen was a Fellow of the American Academy of Family Physicians and a Fellow of the American College of Chest Physicians. He was a member of the American Thoracic Society, the Medical Society of the County of Kings and the Medical Society of the State of New York.

Adolph Herman Emerson, MD, Two Rivers, Wisconsin. Died December 22, 1983; age 90. He was a 1925 graduate of Rush Medical College. Dr Emerson was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Herman Federbush, MD, Long Island City. Died January 31, 1984; age 77. He was a 1937 alumnus of Friedrich-Wilhelms-Universität Medizinische Fakultät, Berlin, Prussia. Dr Federbush was a member of the Medical Society of the County of Queens and the Medical Society of the State of New York.

Robert Hugh Feldman, MD, Hallandale, Florida. Died March 24, 1984; age 86. Dr Feldman was a 1922 alumnus of Columbia University College of Physicians and Surgeons. He was a member of the Nassau County Medical Society and the Medical Society of the State of New York.

Sigmund Forster, MD, Brooklyn. Died March 10, 1984; age 78. He was a 1930 alumnus of Università di Napoli Facoltà di Medicina e Chirurgia. Dr Forster was a Fellow of the American College of Physicians and a Diplomate of the American Board of Physical Medicine and Rehabilitation. His memberships included the Academy of Medicine, the New York Society for Physical Medicine and Rehabilitation, the American Academy of Physical Medicine and Rehabilitation, the American Public Health Association, the Medical Society of the County of Kings and the Medical Society of the State of New York.

Olga Frankel, MD, Forest Hills. Died March 19, 1984; age 71. Dr Frankel was a 1938 graduate of the New York University College of Medicine. Her memberships included the American Psychiatric Association, the American Medical Women's Association, the American Academy of Child Psychiatry, the American Public Health Association, the Medical Society of the County of Queens and the Medical Society of the State of New York.

Jacob Friedman, MD, New York. Died March 20, 1984; age 86. He was a 1922 graduate of the New York University College of Medicine. Dr Friedman was a Fellow of the American College of Surgeons and a member of the Academy of Medicine, the New York County Medical Society and the Medical Society of the State of New York.

Irving George Fuhr, MD, Brooklyn. Died November 7, 1983; age 80. Dr Fuhr was a 1928 graduate of New York Medical College, Flower and Fifth Avenue Hospitals. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Joseph Galasso, MD, Savannah, Georgia. Died November 3, 1982; age 76. Dr Galasso was a 1930 graduate of New York Medical College, Flower and Fifth Avenue Hospitals. He was a member of the New York County Medical Society and the Medical Society of the State of New York.

Samuel Stanley Geller, MD, New York. Died January 23, 1984; age 82. Dr Geller was a 1927 alumnus of Tufts University School of Medicine. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Wendell Dow George, MD, Ormond Beach, Florida. Died May 3, 1984; age 82. Dr George was a 1926 graduate of Harvard Medical School. He was a member of the Medical Society of the County of Jefferson and the Medical Society of the State of New York.

Frederick J. Gerstel, MD, New York. Died February 25, 1984; age 80. He was a 1929 alumnus of the Medizinische Fakultät der Universität, Vienna. Dr Gerstel was a Fellow of the American College of Surgeons and a Diplomate of the American Board of Ophthalmology. His memberships included the New York Society for Clinical Ophthalmology, the American Academy of Ophthalmology and Otolaryngology, the New York County Medical Society and the Medical Society of the State of New York.

Anthony R. Giambalvo, MD, Westlake Village, California. Died March 4, 1984; age 83. He was a 1925 graduate of the State University of New York Downstate Medical Center. Dr Giambalvo was a member of the Medical Society of the County of Queens and the Medical Society of the State of New York.

William Vincent Gilbert, MD, New York. Died April 2, 1984; age 84. Dr Gilbert was a 1924 alumnus of Eclectic Medical College. He was a member of the American Academy of Family Physicians, the American Geriatrics Society, the American Public Health Association, the Bronx County Medical Society and the Medical Society of the State of New York.

Ronald Giovannelli, MD, Bayville. Died January 17, 1984; age 75. He was a 1934 graduate of Università di Napoli Facoltà di Medicina e Chirurgia. Dr Giovannelli was a member of the Academy of Medicine, the Medical Society of the County of Oswego and the Medical Society of the State of New York.

Martin Zerega Glynn, MD, Syosset. Died March 20, 1984; age 76. He was a 1933 alumnus of Georgetown University School of Medicine. Dr Glynn was a Fellow of the American College of Obstetricians and Gynecologists and a Fellow of the American College of Surgeons. He was a member of the Pan American Medical Association, the Medical Society of the County of Kings and the Medical Society of the State of New York.

Morris C. Goldberg, MD, Jamaica. Died February 16, 1984; age 77. He was a 1930 alumnus of Columbia University College of Physicians and Surgeons. Dr Goldberg was a Fellow of the American Academy of Family Physicians and a Diplomate of the American Board of Family Practice. His memberships included the American Geriatrics Society, the Medical Society of the County of Kings and the Medical Society of the State of New York.

Hans H. T. Goldmann, MD, Nahariya, Israel. Died November 4, 1982; age 87. He was a 1923 graduate of Universität Leipzig Medizinische Fakultät, Saxony. Dr Goldmann was a member of the New York County Medical Society and the Medical Society of the State of New York.

Charles Muller Graney, MD, Batavia. Died April 11, 1984; age 79. He was a 1930 graduate of Harvard Medical School. Dr Graney was a Fellow of the American College of Surgeons. He was a member of the Medical Society of the County of Genesee and the Medical Society of the State of New York.

Justin L. Greene, MD, Patterson. Died March 1, 1984; age 74. He was a 1938 graduate of the Université de Paris Faculté de Médecine. Dr Greene was a Diplomate of the American Board of Psychiatry and Neurology. His memberships included the Academy of Medicine, the American Psychiatric Association, the Association for Research in Nervous and Mental Disease, the New York County Medical Society and the Medical Society of the State of New York.

George M. Hadda, MD, Forest Hills. Died January 10, 1984; age 69. Dr Hadda was a 1939 alumnus of Schlesische-Friedrich-Wilhelms-Universität Medizinische Fakultät, Breslau, Prussia. He was a Qualified Fellow of the International College of Surgeons and a Diplomate of the American Board of Surgery. His memberships included the American Society of Abdominal Surgeons, the Medical Society of the County of Queens and the Medical Society of the State of New York.

George Hugo Hagen, MD, Indianapolis, Indiana. Died March 14, 1984; age 86. Dr Hagen was a 1923 alumnus of Hamburgische Universität Medizinische Fakultät, Hamburg. He was a member of the Medical Society of the County of Queens and the Medical Society of the State of New York.

Emmy Hahn, MD, New York. Died September 19, 1983; age 82. Dr Hahn was a 1929 alumna of Ludwig-Maximilians-Universität Medizinische, München, Bavaria. She was a member of the New York County Medical Society and the Medical Society of the State of New York.

Ellwyn Emery Heier, MD, Cattaraugus. Died April 26, 1984; age 78. Dr Heier was a 1931 graduate of the University of Buffalo School of Medicine and was a member of the Medical Society of the County of Cattaraugus and the Medical Society of the State of New York.

Armand Herbert Hoch, MD, Oriskany Falls. Died April 9, 1984; age 65. He was a 1945 alumnus of New York Medical College, Flower and Fifth Avenue Hospitals. Dr Hoch was a member of the Medical Society of the County of Oneida and the Medical Society of the State of New York.

Peter A. Ierardi, Jr, MD, Palm Bay, Florida. Died December 3, 1983; age 67. Dr Ierardi was a 1943 alumnus of Georgetown University School of Medicine. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Salvatore Invidiata, MD, Rockaway Point. Died December 22, 1983; age 74. Dr Invidiata was a 1936 graduate of New York Medical College, Flower and Fifth Avenue Hospitals. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Morris Jacoff, MD, Far Rockaway. Died March 9, 1983; age 92. He was a 1915 alumnus of the State University of New York Downstate Medical Center. Dr Jacoff was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Bernard S. Kahn, MD, New York. Died September 7, 1983; age 79. He was a 1927 alumnus of George Washington University School of Medicine. Dr Kahn was a Fellow of the American College of Physicians and a Diplomate of the American Board of Internal Medicine. His memberships included the Academy of Medicine, the International Society of Hematology, the American Geriatrics Society, the New York County Medical Society and the Medical Society of the State of New York.

Irving Louis Kaplan, MD, Woodbury. Died May 6, 1984; age 71. Dr Kaplan was a 1943 alumnus of Middlesex University School of Medicine. His memberships included the American Psychiatric Association, the Nassau County Medical Society and the Medical Society of the State of New York.

Murray Bernard Klayman, MD, Huntington. Died March 28, 1984; age 57. Dr Klayman was a 1956 alumnus of Universität Bern Medizinische Fakultät. His memberships included the New York Otological Society, the American Academy of Facial Plastic and Reconstructive Surgery, the American Geriatrics Society, the Suffolk County Medical Society and the Medical Society of the State of New York.

Hilde Gertrud Koppel, MD, White Plains. Died March 5, 1984; age 74. She was a 1938 alumna of Universität Bern Medizinische Fakultät. Dr Koppel was a member of the American Psychiatric Association, the American Psychoanalytic Association, the Medical Society of the County of Westchester and the Medical Society of the State of New York.

Charles H. Kosmaler, MD, Elmira. Died April 1, 1984; age 75. He was a 1936 graduate of the University of Rochester School of Medicine and Dentistry. Dr Kosmaler was a Fellow of the American College of Physicians, a Fellow of the American College of Chest Physicians and a Diplomate of the American Board of Internal Medicine. He was a member of the Medical Society of the County of Chemung and the Medical Society of the State of New York.

Daniel Kravitz, MD, Long Beach. Died January 10, 1984; age 87. He was a 1921 graduate of New York University College of Medicine. Dr Kravitz was a Fellow of the American College of Surgeons and a Diplomate of the American Board of Ophthalmology. His memberships included the New York Society for Clinical Ophthalmology, the American Academy of Ophthalmology and Otolaryngology, the Pan American Association of Ophthalmology, the Medical Society of the County of Kings and the Medical Society of the State of New York.

Harry G. Kupperman, MD, Hallandale, Florida. Died April 12, 1984; age 83. He was a 1925 graduate of Columbia University College of Physicians and Surgeons. Dr Kupperman was a member of the New York County Medical Society and the Medical Society of the State of New York.

Charles S. Labriola, MD, North Haven. Died November 30, 1981; age 73. He was a 1935 alumnus of the State University of New York Downstate Medical Center. Dr Labriola was a Fellow of the American College of Surgeons, a Qualified Fellow of the International College of Surgeons, and a Diplomate of the American Board of Ophthalmology. He was a member of the American Academy of Ophthalmology and Otolaryngology, the Medical Society of the County of Kings and the Medical Society of the State of New York.

Benjamin E. Lanier, MD, Brooklyn. Died March 19, 1984; age 62. Dr Lanier was a 1952 alumnus of the Université de Lausanne Faculté de Médecine. He was a Fellow of the American College of Surgeons and a Diplomate of the American Board of Orthopedic Surgery. His memberships included the Academy of Medicine, the American Academy of Orthopaedic Surgeons, the Medical Society of the County of Kings and the Medical Society of the State of New York.

Samuel Leo, MD, Palo Alto, California. Died November 7, 1983; age 84. He was a 1923 alumnus of the State University of New York Downstate Medical Center. Dr Leo was a Fellow of the American College of Surgeons and a member of the Bronx County Medical Society and the Medical Society of the State of New York.

Thurber LeWin, MD, Buffalo. Died May 12, 1984; age 87. Dr LeWin was a 1921 graduate of the University of Buffalo School of Medicine. He was a Fellow of the American College of Surgeons and a Diplomate of the American Board of Ophthalmology. His memberships included the American Academy of Ophthalmology and Otolaryngology, the Medical Society of the County of Erie and the Medical Society of the State of New York.

Harvey Lozman, MD, New York. Died April 17, 1984; age 47. He was a 1962 graduate of Jefferson Medical College of Philadelphia. Dr Lozman was a Fellow of the American College of Surgeons and a Diplomate of the American Board of Surgery. He was a member of the New York State Surgical Society, the New York County Medical Society and the Medical Society of the State of New York.

Laurence S. MacMillan, MD, Utica. Died March 30, 1984; age 87. He was a 1923 graduate of the State University of New York Upstate Medical Center. Dr MacMillan was a member of the Academy of Medicine, the Medical Society of the County of Oneida and the Medical Society of the State of New York.

Frederick B. MacNaughton, MD, Millbrae, California. Died July 23, 1983; age 87. He was a 1920 alumnus of Albany Medical College of Union University. Dr MacNaughton was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

David Marcus, MD, New York. Died January 28, 1984; age 76. He was a 1932 graduate of New York Medical College, Flower and Fifth Avenue Hospitals. Dr Marcus was a Fellow of the American Academy of Family Physicians and a Diplomate of the American Board of Family Practice. He was a member of the American Geriatrics Society, the Medical Society of the County of Kings and the Medical Society of the State of New York.

Alfred Francis Marra, MD, Bronx. Died April 14, 1984; age 80. He was a 1929 alumnus of New York University College of Medicine. Dr Marra was a Fellow of the American College of Cardiology, a Fellow of the American College of Physicians and a Diplomate of the American Board of Internal Medicine. He was a member of the American Geriatrics Society, the Bronx County Medical Society and the Medical Society of the State of New York.

Edwin Post Maynard, MD, Brooklyn. Died May 9, 1984; age 92. He was a 1919 alumnus of Columbia University College of Physicians and Surgeons. Dr Maynard was a Fellow of the American College of Physicians and a Diplomate of the American Board of Internal Medicine. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Peter Mombello, MD, Fishkill. Died April 23, 1984; age 78. Dr Mombello was a 1930 graduate of New York University College of Medicine. He was a Qualified Fellow of the International College of Surgeons. His memberships included the American Geriatrics Society, the International Academy of Proctology, the Dutchess County Medical Society and the Medical Society of the State of New York.

Charles Robert Neier, MD, Bayside. Died February 19, 1984; age 67. He was a 1940 alumnus of the State University of New York Upstate Medical Center. Dr Neier was a Fellow of the American College of Surgeons and a Diplomate of the American Board of Urology. He was a member of the American Urological Association, the Medical Society of the County of Queens and the Medical Society of the State of New York.

Lewis Alfred Newfield, MD, Belle Harbor. Died March 9, 1984; age 95. He was a 1915 graduate of Columbia University College of Physicians and Surgeons. Dr Newfield was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

George Hunter O'Kane, MD, New York. Died April 14, 1984; age 83. He was a 1931 graduate of the University of Rochester School of Medicine and Dentistry. Dr O'Kane was a Diplomate of the American Board of Otolaryngology. He was a member of the American Academy of Otolaryngology, the New York County Medical Society and the Medical Society of the State of New York.

Panfilio B. Ozaeta, Jr, MD, Old Westbury. Died April 8, 1983; age 43. Dr Ozaeta was a 1963 graduate of the University of Santo Tomas Faculty of Medicine and Surgery, Manila. He was a member of the Nassau County Medical Society and the Medical Society of the State of New York.

Albert Piket, MD, Setauket. Died January 5, 1984; age 76. He was a 1934 graduate of the Medizinische Fakultät der Universität, Vienna. Dr Piket was a Fellow of the American College of Anesthesiologists. He was a member of the New York State Society of Anesthesiologists, the American Society of Anesthesiologists, Inc, the Medical Society of the County of Queens and the Medical Society of the State of New York.

Daniel Edward Quinlan, MD, Tampa, Florida. Died January 4, 1984; age 83. Dr Quinlan was a 1928 graduate of Georgetown University School of Medicine. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Tony Liebman Rakieten, MD, Bay Shore. Died April 22, 1984; age 82. He was a 1929 graduate of Yale University School of Medicine. Dr Rakieten was a member of the Society of American Bacteriologists, the Suffolk County Medical Society and the Medical Society of the State of New York.

Beulah Richard H. Rhoden, MD, Bronx. Died July 13, 1983; age 90. Dr Rhoden was a 1921 graduate of the University of Pennsylvania School of Medicine and was a member of the New York County Medical Society and the Medical Society of the State of New York.

Solomon S. Rinkoff, MD, Hallandale, Florida. Died April 10, 1984; age 90. He was a 1919 alumnus of the State University of New York Downstate Medical Center. Dr Rinkoff was a member of the Bronx County Medical Society and the Medical Society of the State of New York.

Eli G. Rochelson, MD, Brooklyn. Died February 12, 1984; age 77. He was a 1940 alumnus of Vytauto Didziojo Universiteto Medicinos Fakulteto, Kaunas. Dr Rochelson was a Fellow of the American College of Chest Physicians. He was a member of the American Thoracic Society, the Medical Society of the County of Kings and the Medical Society of the State of New York.

Rebecca Teichman Roman, MD, Roslyn. Died March 2, 1984; age 91. She was a 1916 alumna of New York Medical College and Hospital for Women. Dr Roman was a member of the Medical Society of the County of Queens and the Medical Society of the State of New York.

Benjamin Rosenthal, MD, East Rockaway. Died December 31, 1977; age 90. Dr Rosenthal was a 1909 alumnus of the State University of New York Downstate Medical Center. He was a member of the New York Cardiological Society, the New York County Medical Society and the Medical Society of the State of New York.

Melvin E. Rossman, MD, Islip Terrace. Died April 26, 1984; age 56. Dr Rossman was a 1951 alumnus of the State University of New York Upstate Medical Center. His memberships included the New York State Society of Internal Medicine, the International Academy of Proctology, the American Geriatrics Society, the American Society of Internal Medicine, the Suffolk County Medical Society and the Medical Society of the State of New York.

Anthony William Russo, MD, Woodhaven. Died February 29, 1984; age 75. Dr Russo was a 1933 graduate of the State University of New York Downstate Medical Center. He was a member of the Medical Society of the County of Queens and the Medical Society of the State of New York.

Raymond Charles Ryan, MD, Garden City. Died February 19, 1984; age 76. He was a 1934 graduate of the State University of New York Downstate Medical Center. Dr Ryan was a Fellow of the American College of Cardiology, a Fellow of the American College of Physicians, a Fellow of the American College of Chest Physicians, and a Diplomate of the American Board of Internal Medicine. His memberships included the New York Cardiological Society, the American Thoracic Society, the American Geriatrics Society, the Medical Society of the County of Queens and the Medical Society of the State of New York.

Herta Seidemann, MD, New York. Died March 21, 1984; age 84. She was a 1926 graduate of Schlesische-Friedrich-Wilhelms-Universität Medizinische Fakultät, Breslau, Prussia. Dr Seidemann was a Diplomate of the American Board of Psychiatry and Neurology. She was a member of the American Psychiatric Association, the New York County Medical Society and the Medical Society of the State of New York.

Alexander N. Selman, MD, Hollywood, Florida. Died December 28, 1983; age 84. He was a 1921 graduate of Fordham University School of Medicine. Dr Selman was a Fellow of the American College of Surgeons and a Qualified Fellow of the International College of Surgeons. He was a member of the Academy of Medicine, the Medical Society of the County of Rockland and the Medical Society of the State of New York.

Eldred Joseph Stevens, MD, Ormond Beach, Florida. Died April 23, 1984; age 76. Dr Stevens was a 1934 alumnus of the State University of New York Upstate Medical Center. He was a member of the Steuben County Medical Society and the Medical Society of the State of New York.

Franz Sales Stieglmayr, MD, Elmhurst. Died January 3, 1984; age 65. Dr Stieglmayr was a 1948 alumnus of the Medizinische Fakultät der Universität, Vienna. He was a Diplomate of the American Board of Psychiatry and Neurology. He was a member of the American Academy of Neurology, the Medical Society of the County of Queens and the Medical Society of the State of New York.

Abraham Bernard Susman, MD, New York. Died March 1, 1984; age 81. He was a 1928 alumnus of Queens University Faculty of Medicine. Dr Susman was a Diplomate of the American Board of Pediatrics. He was a member of the New York County Medical Society and the Medical Society of the State of New York.

Edward Michael Tapper, MD, New York. Died December 8, 1983; age 87. Dr Tapper was a 1923 graduate of the State University of New York Downstate Medical Center. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Nathaniel Tatkow, MD, Dunedin, Florida. Died December 2, 1983; age 79. Dr Tatkow was a 1931 graduate of St. Louis University School of Medicine. He was a member of the American Geriatrics Society, the Medical Society of the County of Kings and the Medical Society of the State of New York.

William F. Tracy, MD, Rome. Died March 29, 1984; age 73. Dr Tracy was a 1938 graduate of the State University of New York Upstate Medical Center. He was a member of the Medical Society of the County of Oneida and the Medical Society of the State of New York.

Joseph John Toye, MD, Bayport. Died February 22, 1984; age 66. Dr Toye was a 1942 graduate of Columbia University College of Physicians and Surgeons. He was a member of the American Academy of Family Physicians, the Suffolk County Medical Society and the Medical Society of the State of New York.

Glenn W. Tymeson, MD, Endwell. Died May 5, 1984; age 66. He was a 1944 graduate of Jefferson Medical College of Philadelphia. Dr Tymeson was a Fellow of the American Academy of Family Physicians and a Diplomate of the American Board of Family Practice. He was a member of the Broome County Medical Society and the Medical Society of the State of New York.

Frits Albert Van Gessel, MD, Flushing. Died March 18, 1984; age 60. Dr Van Gessel was a 1953 graduate of Universiteit van Amsterdam Geneeskunde Faculteit, The Netherlands. His memberships included the American Fertility Society, the American Society of Abdominal Surgeons, the Medical Society of the County of Queens and the Medical Society of the State of New York.

Oscar N. Vazquez-Castro, MD, Flushing. Died April 2, 1984; age 62. Dr Vazquez-Castro was a 1961 alumnus of the University of Puerto Rico School of Medicine. He was a member of the Society of Nuclear Medicine, the New York County Medical Society and the Medical Society of the State of New York.

Stephen J. Walker, MD, New York Mills. Died February 23, 1984; age 87. Dr Walker was a 1923 graduate of Ludwig-Maximilians-Universität Medizinische Fakultät, Munchen, Bavaria. His memberships included the Academy of Medicine, the American Rheumatism Association, the American Academy of Family Physicians, the Medical Society of the County of Oneida and the Medical Society of the State of New York.

Arthur J. Wallingford, MD, Albany. Died February 6, 1984; age 86. Dr Wallingford was a 1927 alumnus of the Albany Medical College of Union University. He was a Fellow of the American College of Surgeons, a Fellow of the American College of Obstetricians and Gynecologists, a Qualified Fellow of the International College of Surgeons, and a Diplomate of the American Board of Obstetrics and Gynecology. His memberships included the Academy of Medicine, the Medical Society of the County of Albany, and the Medical Society of the State of New York.

Joseph Patrick Zaia, MD, Rochester. Died February 4, 1984; age 48. He was a 1962 alumnus of Georgetown University School of Medicine. Dr Zaia was a Diplomate of the American Board of Internal Medicine, and a member of the American Rheumatism Association, the Medical Society of the County of Monroe, and the Medical Society of the State of New York.

Guidelines for authors

ORIGINALITY

The *New York State Journal of Medicine* welcomes research papers and original essays on the practice of medicine, medical education, public health, the history of medicine, medicolegal matters, legislation, ethics, the mass media and socioeconomic issues in health care.

Manuscripts should be prepared according to the "Uniform requirements for manuscripts submitted to biomedical journals" (*NY State J Med* 1983; 83:1089-1094). The requirements were established by the International Committee of Medical Journal Editors, of which the *Journal* is a participating member. These Guidelines are intended to highlight aspects of the *Journal*'s particular style of publication.

A manuscript will be considered for publication if it is original, has not been published previously in whole or in part in either a medical journal or a lay publication, and is not simultaneously under consideration elsewhere. A copy of any possibly duplicative material, such as a reference "in press," should be submitted along with the manuscript.

PREPARATION

An original typewritten or "word-processed" manuscript and two photocopies (to facilitate outside review) are required. If the manuscript is not accepted for publication, the original and one copy will be returned. All figures must be submitted in triplicate. The manuscript should be double-spaced throughout, including references, tables, legends, quotations, and acknowledgments. A separate title page should include the full title of the paper in upper and lower case type, the names of the authors exactly as they should appear in print (including their highest academic degree), an abbreviated title of no greater than 40 spaces for use as a running foot, and the names of all providers of funding for research on which the paper is based. Information on the amount and allocation of funding is optional.

A corresponding author should be designated in the covering letter. Authors should list their title and affiliation at the time they did the work, and, if different, their present affiliation. The addresses and telephone numbers of all authors should be supplied for editorial purposes. All authors of a manuscript are responsible for having read and approved it for submission.

CATEGORIES

Research Papers should be limited to 2,500 words and should include the following sections: Introduction, Methods, Results, Discussion, and References. Multiple subheadings and numbered lists are discouraged. An abstract limited to 150 words should state the reasons for the study, the main findings, and their implications. Statistical evaluations should be described in the Methods section, and the name and affiliation of the statistician should be included in the acknowledgments if this individual is not listed as a coauthor. Reports of experiments involving human subjects must include a description in the Methods section of the informed consent obtained and a statement that the procedures followed were approved by an institutional research review committee. Anonymity of patients must be preserved. Reports of experiments on animals must note which guidelines were followed for the care and use of laboratory animals.

Case Reports should be limited to 1,250 words. Review Articles should not exceed 3,000 words. Commentaries should be between 750 and 1,000 words. Other kinds of original essays should not exceed 2,000 words. A letter of inquiry should be sent to the editor prior to submitting a Review Article or Commentary.

For Research Papers only, scientific measurements should be given in conventional units, with Système Internationale (SI) units in parentheses. Abbreviations and acronyms should be kept to a minimum, and jargon should be avoided. Generic names of drugs should be used instead of brand names.

FIGURES

The submission of color illustrations or slides is discouraged. Only black and white glossy photographic prints or "camera-ready" artwork will be accepted. The *Journal* is unable to provide art services such as the addition of arrows to photographs. A signed consent for publication must accompany photographs in which the patient is identifiable. Illustrations from other publications generally will not be considered. Legends for illustrations should be typed on a separate sheet, and for photomicrographs should include magnification and stain. Each illustration should be lightly marked on the back in pencil with the name of the first author, the number as cited in the text, and an arrow indicating the top. Each set of illustrations should be submitted unmounted in a separate envelope.

Tables should be simple, self-explanatory, and few in number. Each table should be typed double-spaced on a separate sheet.

REFERENCES

References should be limited to the most pertinent. The recommended maximum number of references is 25 for Research Papers and most other original contributions (except lengthier Review Articles), 12 for Commentaries and Case Reports, and six for letters to the editor.

Authors are responsible for the accurate citation of references. Citation of secondary sources is discouraged except where the original reference is unobtainable. Authors may not cite references they have not read, and the use of abstracts as references should be avoided.

References should be indicated in the text by superscript numbers following the name of the author (eg, Smith^2 reported two cases).

The list of references at the end of the article should be typed double-spaced and references should be numbered in the order in which they appear on the text. When there are six or fewer authors, all should be listed; where there are seven or more, the first three should be listed, followed by *et al.* Names of journals should be abbreviated according to *Index Medicus* and underlined.

Sample references:

1. Kepes ER, Thomas P, Vemulapalli K: Methadone and intravenous morphine requirements. *NY State J Med* 1983; 83:925-927.
2. McGuigan JE. Peptic ulcer. In: Petersdorf RG, Adams RD, Braunwald E, Isselbacher KJ, Martin JB, Wilson JD, eds. *Harrison's Principles of Internal Medicine.* New York, McGraw-Hill, 1983, pp 1697-1712.

REVIEW

All manuscripts are reviewed by the editors, and most manuscripts are sent to outside referees. Decisions concerning acceptance, revision, or rejection of a manuscript are usually made within three to six weeks. Every effort will be made to assure prompt publication of an accepted manuscript. A galley proof will be sent to the author for approval prior to publication.

Address correspondence to Alan Blum, MD, Editor, *New York State Journal of Medicine*, P.O. Box 5404, 420 Lakeville Road, Lake Success, NY 11042.

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For further information contact:
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Aged. 2 Cat 1 credits. *Oct 18.* **Senile Dementia.** 2 Cat 1 credits. *Oct 25.* **Diagnosis and Treatment of Headache.** 2 Cat 1 credits. Westchester Square Hospital, Bronx. Info: CME Westchester Square Hospital/Albert Einstein College of Medicine/Montefiore Medical Center, 2475 St. Raymond Avenue, Bronx, NY 10461. Tel: (212) 828-6600.

BROOKLYN

Oct 17. **Neurology-Nephrology, "A Neurologist Looks at a Kidney."** 8 Cat 1 credits. Info: Dr Walter R. Slade, Jr, Chief, Neurology Service, VA Medical Center, 800 Poly Place, Brooklyn, NY 11209. Tel: (212) 836-6600, ext 562.

BROOME

Oct 3. **Geriatric Teaching Day.** 6 Cat 1 credits. *Oct 13.* **7th Annual Gastroenterology Teaching Day.** 7 Cat 1 credits. *Oct 24.* **Annual Dental Teaching Day.** 6 Cat 1 credits. Binghamton General Hospital. Info: Sandy Cook, CME Coordinator, Mitchell Ave, Binghamton, NY 13903. Tel: (607) 771-2549.

MONROE

Oct 18. **Practical Use of the Laboratory in Diagnosis and Management of Rheumatic Disease.** Rochester. Info: Alessandro Bertoni, MD, Park Ridge Hospital, 1555 Long Pond Road, Rochester, NY 14626. Tel: (716) 325-4044.

Oct 22-26. **1984 Postgraduate Course in Clinical Pharmacology, Drug Development, and Regulation.** Rochester. Info: Kristine Niven, Center for the Study of Drug Development, The University of Rochester Medical Center, 601 Elmwood Ave, Rochester, NY 14642. Tel: (716) 275-4003.

ONONDAGA

Oct 19-21. **VII Annual Symposium in Radiology, Neoplastic Disease, Radiological and Clinical Interactions.** Syracuse. Info: Program Coordinator, Office of Continuing Education, Upstate Medical Center, SUNY 750 E Adams St, Syracuse, NY 13210. Tel: (315) 473-4606.

ROCKLAND

Oct 10. **Advances in the Recognition and Management of Cardiac Arrhythmias.** 3 Cat 1 credits. Suffern. Info: Thomas R. Daly, The New York Cardiological Society, Inc, 84 Grove St, Suite 2, New York, NY 10014. Tel: (212) 924-5346.

WESTCHESTER

Oct 3. **Current Issues in Psychiatry.** 6 Cat 1 credits. Tarrytown. Info: Beth Davies, RN, Assistant Director of Medical Education, Harlem Valley Psychiatric Center, Wingdale, NY 12594. Tel: (914) 832-6611.

Oct 17. **Eighth Annual Day in Cardiology.** 6 Cat 1 credits. White Plains Hospital Medical Center. Info: Toni Calabrese Boelsen, Director of Public Relations, White Plains Hospital Medical Center, White Plains, NY 10601. Tel: (914) 681-1118.

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Navy Medical Programs
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Tarrytown Hilton Hotel. Info: Page & William Black Post-Graduate School of Medicine, One Gustave L. Levy Place, New York, NY 10029. Tel: (212) 650-6737.

AROUND THE NATION

DISTRICT OF COLUMBIA

Oct 11-12. **Advances in Gynecologic Oncology and Gynecologic Surgery.** 11 Cat 1 credits. Ramada Renaissance Hotel. Info: Office of Continuing Medical Education, Georgetown University School of Medicine, First Floor-Hospital, 3800 Reservoir Road, NW, Washington, DC 20007. Tel: (202) 625-2306.

FLORIDA

Oct 15-19. **Family Practice Review.** 26 Cat 1 credits. Buena Vista. Info: Office of Continuing Medical Education of the University of Florida College of Medicine, Box J-233, JHM Health Center, Gainesville, FL 32610. Tel: (904) 392-3143.

HAWAII

Oct 20-27. **Ninth Annual Pediatrics for the Practitioner.** 20 Cat 1 credits. Info: Assistant Director, Center for Health Education, Memorial Medical Center of Long Beach, 2801 Atlantic Avenue, Long Beach, CA 90801-1428.

LOUISIANA

Oct 15-20. **OB/GYN Pathology & Oncology.** 43 Cat 1 credits. New Orleans. Info: Division of CME, Wesley Medical Center, 550 N. Hillside, Wichita, KS 67214. Tel: (316) 688-3316.

MARYLAND

Oct 11-13. **10th Annual Topics in Gastroenterology & Liver Disease: Medical & Surgical Aspects.** 20 Cat 1 credits. The Johns Hopkins University School of Medicine. Info: Program Coordinator, Turner 22, 720 Rutland Ave, Baltimore, MD 21205.

MASSACHUSETTS

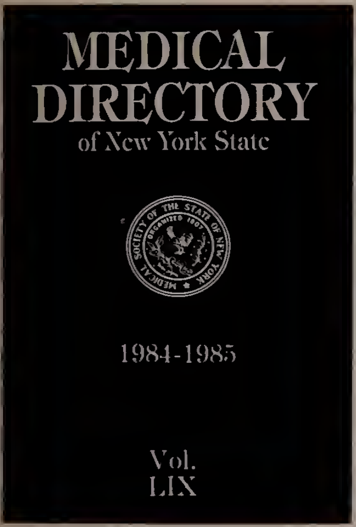
Oct 11-14. **Flexible Fiberoptic Sigmoidoscopy in the Diagnosis of Colorectal Diseases.** Sturbridge. Info: Edward J. Kowalewski, MD, Course Chairman, Seminars & Symposia, Inc, 132 E 70th St, New York, NY 10021. Tel: (212) 517-7520.

Oct 21-Nov 2. **Program for Health Systems Management.** *Oct 30-Nov 1.* **Biological Effects of Ionizing Radiation.** Boston. Info: Dept A, Harvard School of Public Health, 677 Huntington Ave, Boston, MA 02115. Tel: (617) 732-1171.

Oct 25-26. **The Thyroid: A Clinical Approach.** Boston. Info: Harvard Medical School/Massachusetts General Hospital, Department of Continuing Education, Boston, MA 02115. Tel: (617) 732-1525.

MICHIGAN

Oct 25-27. **International Symposium on Implant Surgery for the Hand and Upper Extremity.** Grand Rapids. 18 Cat 1 credits. Info: American Society for Surgery of the Hand, 3025 South Parker



ANNOUNCING THE
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Published, biennially, by the Medical Society of the State of New York, this important, 935 page, reference source will be available in September 1984.

The Directory lists over 27,000 New York State physicians, both members of the Medical Society, and non-members who chose to be listed for a fee. It includes the following data:

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★**O'CONNOR, Robert James,** 33 Valencia Ave 10301. Tel 447-7242. STATE UNIV BKLN 51. D-OG. SL. FACOG. FICS. Am Abdominal Sur. Am Ac Comp Med. Attd O&G Staten Isl. Cons O&G USPHSH SI. Attd Gyn Sea View. Also Lake Success (MEM-AMA)

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Oct 24–27. **The American Academy of Clinical Anesthesiologists Fall Seminar.** 11 Cat 1 credits. Asheville. Info: AACA, Knoxville, TN 37919-1691. Tel: (615) 588-6279.

OHIO

Oct 10–11. **Oncology Update.** 10 Cat 1 credits. Cleveland. Info: The Cleveland Clinic Education Foundation, Room 3T01, 9500 Euclid Ave, Cleveland, OH 44106. Tel: (800) 762-8173.

Oct 13–21. **Comprehensive OB/GYN Conference.** Columbus. 78 Cat 1 credits. Info: Perinatal Resources, Inc. 2410 Coventry Rd, Columbus, OH 43221. Tel: (800) 424-6903.

PENNSYLVANIA

Oct 22–26. **Concepts in Obstetrics and Gynecology.** 32½ Cat 1 credits. University of Pennsylvania. Info: Office of Continuing Medical Education, School of Medicine/G-3, University of Pennsylvania, Philadelphia, PA 19104.

TEXAS

Oct 13–14. **Reading a Chest X-Ray—An Integrated Anatomical, Physiological, Pathological Approach.** 20 Cat 1 credits. Houston. Info: Mary J. Ryals, PO Box 61203, DFW Airport, TX 75261. Tel: (214) 659-9590.

VIRGINIA

Oct 8–10. **The Child and Young Adult: Practical Management of Their Ambulatory Problems.** 15 Cat 1 credits. Arlington. Info: Carol S. Miller, Director of Medical Staff Services & CME Coordinator, The Fairfax Hospital, 3300 Gallows Road, Falls Church, VA 22046. Tel: (703) 698-3101.

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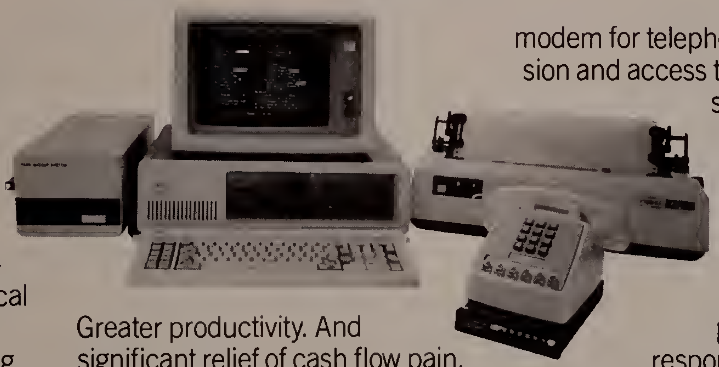

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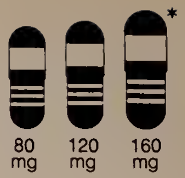
INDERAL® LA

(PROPRANOLOL HCl) LONG ACTING CAPSULES



BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)*

INDERAL* LA brand of propranolol hydrochloride **(Long Acting Capsules)**

DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules

CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product INDERAL LA can provide effective beta blockade for a 24-hour period

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and [illegible]ewhat variable. INDERAL has been shown to cause a small increase in serum potassi[illegible] concentration when use[illegible] the treatment of hypertensive patients

In angina pectoris, propranolol generally reduces t[illegible]n re[illegible]t any given level of effort by blocking the catecholamine[illegible] inc[illegible] the h[illegible] rate, systolic blood pressure, and the velocity and extent o[illegible]rdial [illegible]nolol may increase oxygen requirements by increasing left [illegible]lar t[illegible] length, [illegible]stolic pressure and systolic ejection period The net phy[illegible]e is usually advantageous and is manifested dur[illegible]rcis[illegible]nd increased work capacity.

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-[illegible] or anesthetic-like membrane action which affects th[illegible]c a[illegible]nti[illegible]ig cance of the membrane action in the treatment of a[illegible]ythm[illegible] is [illegible]cer[illegible]

The mechanism of the antimigraine effect of pr[illegible]lished. B[illegible]-adrenergic receptors have been demonstrated in [illegible]pial ves[illegible]

Beta receptor blockade can be useful in con[illegible]ns in [illegible] bec[illegible]path[illegible]r functional changes, sympathetic activity is detri[illegible]so situations in which sympathetic stimulation is vital F[illegible] example, in patients w[illegible] severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL

WARNINGS. CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible)

> IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol

PRECAUTIONS. *General:* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in [illegible] rats [illegible] empl[illegible] doses [illegible] 150 mg/kg/day, there was no evidence of significant [illegible]lated tumorigenic effects at any of the dosage level[illegible]duc[illegible]dies [illegible]mals [illegible] not show any impairment of fertility that was attri[illegible] to th[illegible]

[illegible]ncy: [illegible]ncy Cat[illegible]ry C. INDERAL has been shown to be embryotoxic in [illegible]ies a[illegible]er than the maximum recommended human dose. Th[illegible] are n[illegible] adequ[illegible]d w[illegible]olled studies in pregnant women. INDERAL should be used during [illegible]gnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mot[illegible]s: INDERAL is excreted in human milk. Caution should be exercised when [illegible]DERAL [illegible]dm[illegible]ste[illegible] a [illegible]sing w[illegible]an.

Pe[illegible]ric [illegible]ety a[illegible]ctive[illegible]ss in children have not been established.

[illegible]VE[illegible]SE R[illegible]CTIONS [illegible] ad[illegible]se effects have been mild and transient and have [illegible]rely [illegible]quired [illegible]drav[illegible] of [illegible]er[illegible]y

C[illegible]diovas[illegible] [illegible]brady[illegible]dia[illegible]gestive heart failure; intensification of AV block; hypo[illegible]tensio[illegible] thr[illegible]bo[illegible]urpura, arterial insufficiency, usually of the [illegible]aynaud type.

Central Nervous Syste[illegible] [illegible]headedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia, visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS)

MIGRAINE—*Dosage must be individualized* The initial oral dose is 80 mg INDERAL LA once daily The usual effective dose range is 160-240 mg once daily The dosage may be increased gradually to achieve optimum migraine prophylaxis If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued It may be advisable to withdraw the drug gradually over a period of several weeks

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

*The appearance of INDERAL LA capsules is a registered trademark of Ayerst Laboratories.

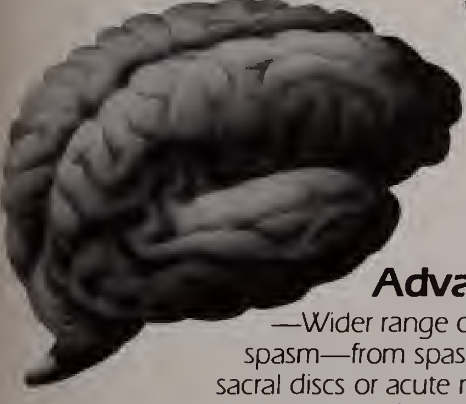
8950/284

Just once each day...

Ayerst. AYERST LABORATORIES
New York, N.Y. 10017

THE SPASM/PAIN/SPASM CYCLE

In skeletal muscle spasm due to local pathology, responsive to the distinct actions of



Adjunctive
VALIUM® (IV)
diazepam/Roche
2-mg, 5-mg, 10-mg scored tablets

Advantages cyclobenzaprine cannot claim

—Wider range of indications as adjunctive therapy for skeletal muscle spasm—from spasm due to local pathology (*e.g.*, herniated lumbosacral discs or acute muscle strain) to spasm associated with upper motor neuron disorders (*e.g.*, cerebral palsy and paraplegia).

—May be used adjunctively for relieving skeletal muscle spasm in patients with hyperthyroidism, cardiac patients and patients being treated with anticholinergics or guanethidine-type antihypertensives.

—Can be administered to patients less than 15 years and more than 6 months of age.

—Scored tablets in three strengths provide greater dosage flexibility.

Since drowsiness, fatigue and ataxia sometimes occur, patients should be cautioned against driving or operating hazardous machinery and should also be advised against simultaneous ingestion of alcohol.

References: 1. Rankin EA: *Contin Educ 3*(1):46-50, Jan 1975. **2.** When muscle spasm hobbles your patient. *Patient Care 8*(11):20-37, Jun 1, 1974.

Valium® (diazepam/Roche) Ⓒ
Before prescribing, please consult complete product information, a summary of which follows:
Indications: Management of anxiety disorders, or short-term relief of symptoms of anxiety Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic Symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal, adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not as sole therapy)
The effectiveness of Valium in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies The physician should periodically reassess the usefulness of the drug for the individual patient
Contraindicated: Known hypersensitivity to the drug Children under 6 months of age Acute narrow angle glaucoma, may be used in patients with open angle glaucoma who are receiving appropriate therapy
Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use, generally at higher therapeutic levels, for at least several months After extended therapy, gradually taper dosage Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence

Usage in Pregnancy: **Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed, drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies Observe usual precautions in impaired renal or hepatic function Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation
The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear
Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported, should these occur, discontinue drug Isolated reports of neutropenia, jaundice, periodic blood counts and liver function tests advisable during long-term therapy
Dosage: Individualize for maximum beneficial effect *Adults* Anxiety disorders, symptoms of anxiety, 2 to 10 mg b.i.d to q.i.d., alcoholism, 10 mg t.i.d. or q.i.d. in first 24 hours, then 5 mg t.i.d or q.i.d as needed, adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d or q.i.d., adjunctively in convulsive disorders, 2 to 10 mg b.i.d to q.i.d *Geriatric or debilitated patients.* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated (See Precautions.) *Children.* 1 to 2½ mg t.i.d or q.i.d initially, increasing as needed and tolerated (not for use under 6 months).
How Supplied: For oral administration, round, scored tablets with a cut out "V" design—2 mg, white; 5 mg, yellow, 10 mg, blue— bottles of 100 and 500, Prescription Paks of 50, available in trays of 10 Tel-E-Dose® packages of 100, available in boxes of 4 reverse-numbered cards of 25, and in boxes containing 10 strips of 10

Imprint on tablets
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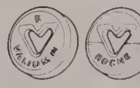
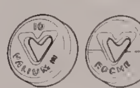
ROCHE (scored side)

5 mg—5 VALIUM® (front)
ROCHE (scored side)



10 mg—10 VALIUM® (front)
ROCHE (scored side)



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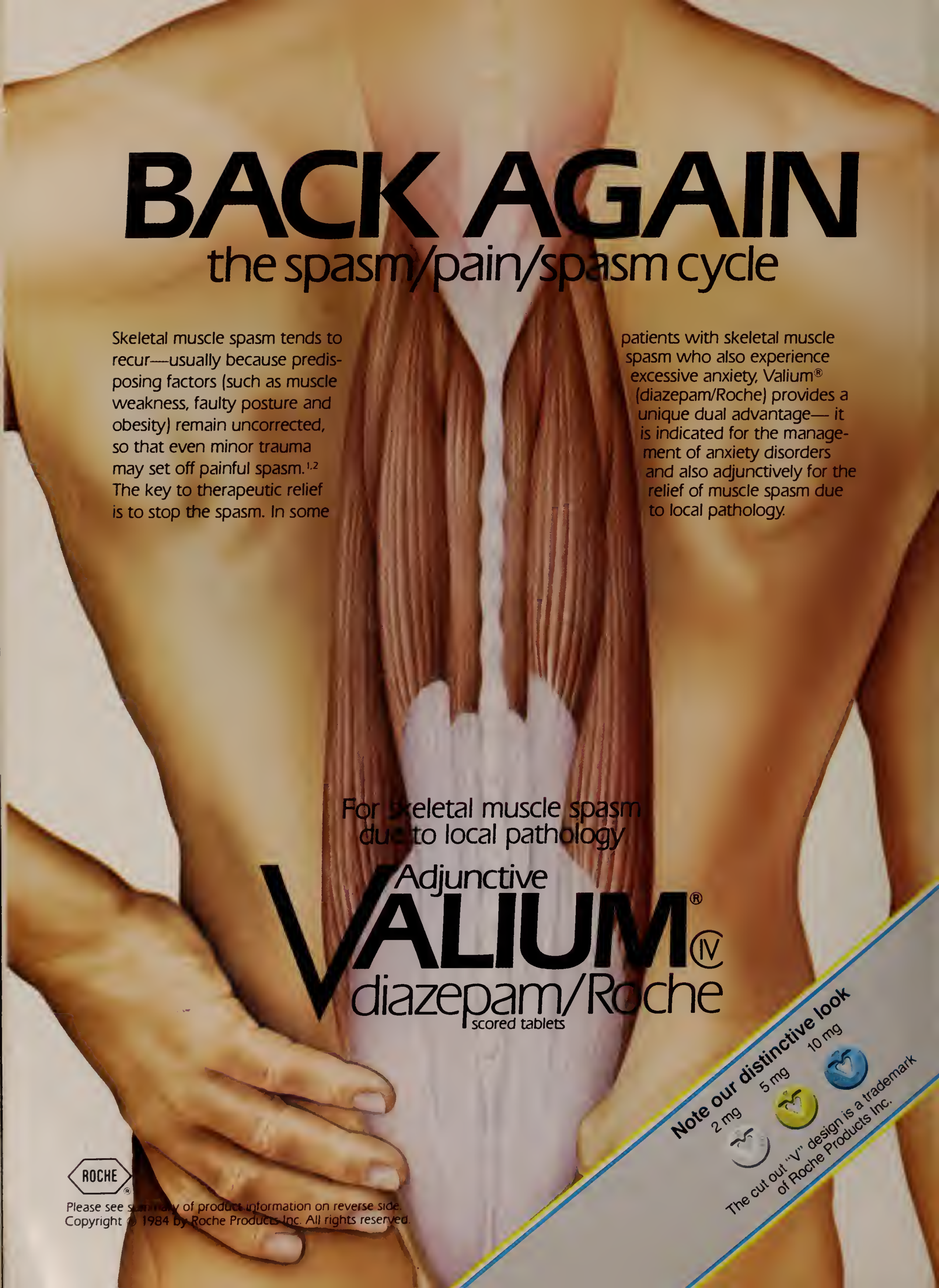

BACK AGAIN

the spasm/pain/spasm cycle

Skeletal muscle spasm tends to recur—usually because predisposing factors (such as muscle weakness, faulty posture and obesity) remain uncorrected, so that even minor trauma may set off painful spasm.[1,2] The key to therapeutic relief is to stop the spasm. In some patients with skeletal muscle spasm who also experience excessive anxiety, Valium® (diazepam/Roche) provides a unique dual advantage— it is indicated for the management of anxiety disorders and also adjunctively for the relief of muscle spasm due to local pathology.

For skeletal muscle spasm due to local pathology

Adjunctive
VALIUM® Ⓘⓥ
diazepam/Roche
scored tablets

Note our distinctive look
2 mg 5 mg 10 mg
The cut out "V" design is a trademark of Roche Products Inc.

ROCHE®

Please see summary of product information on reverse side.

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NEW YORK STATE JOURNAL OF MEDICINE

OCTOBER 1984 • Volume 84, Number 10

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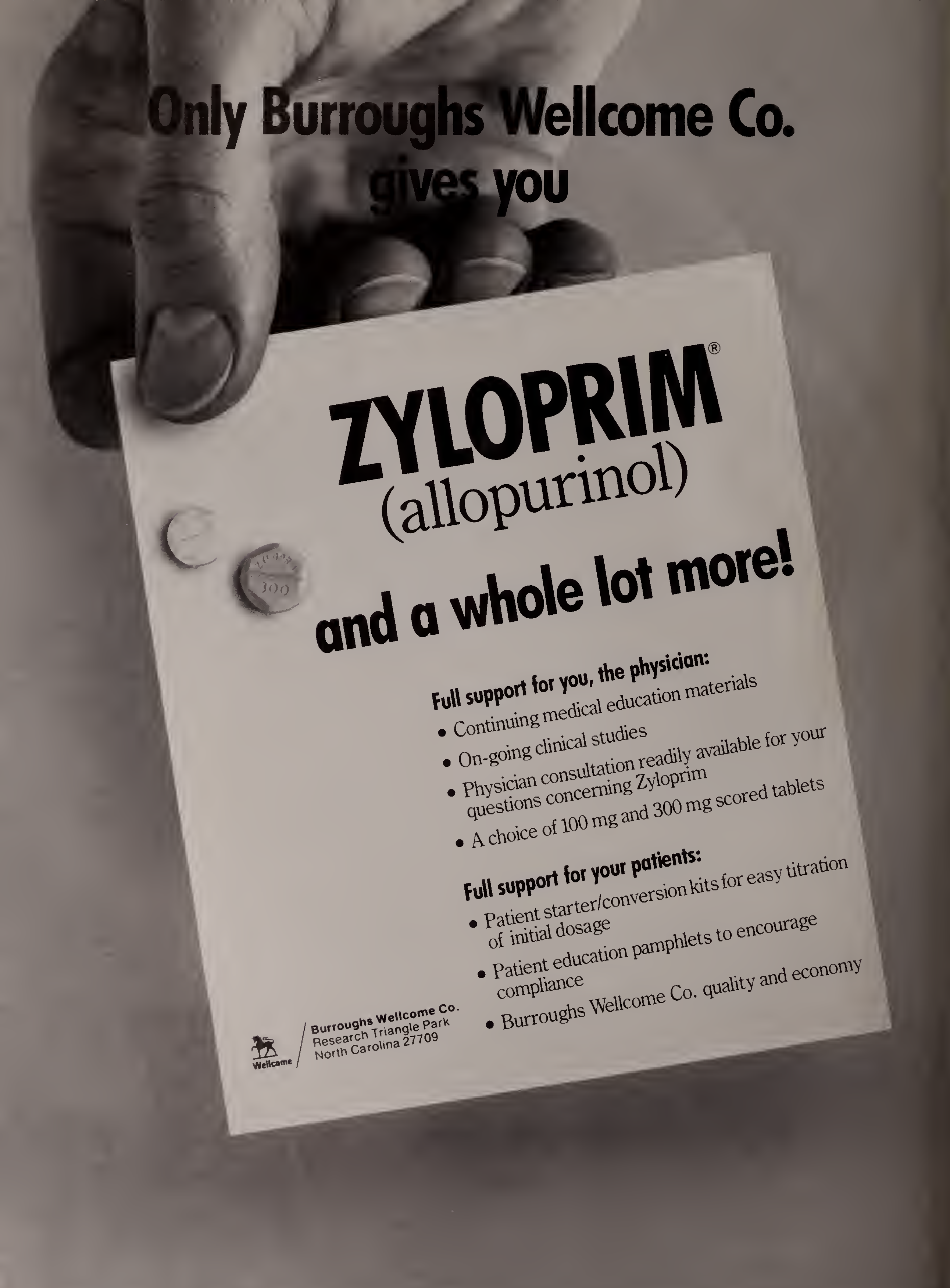

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BALANCED CALCIUM CHANNEL BLOCKADE!

Low incidence of side effects
CARDIZEM® (diltiazem HCl) produces an incidence of adverse reactions not greater than that reported with placebo therapy, thus contributing to the patient's sense of well-being.

*Cardizem is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

References.
1. Strauss WE, McIntyre KM, Parisi AF, et al: Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris. Report of a cooperative clinical trial. Am J Cardiol 49:560-566, 1982.
2. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. Chest 78 (July suppl):234-238, 1980.

Reduces angina attack frequency*
42% to 46% decrease reported in multicenter study.[1]

Increases exercise tolerance*
In Bruce exercise test,[2] control patients averaged 8.0 minutes to onset of pain; Cardizem patients averaged 9.8 minutes ($P<.005$).

CARDIZEM®
(diltiazem HCl)

THE BALANCED
CALCIUM CHANNEL BLOCKER

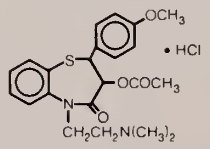
Please see full prescribing information on following page. 2/84

PROFESSIONAL USE INFORMATION

cardizem®
(diltiazem HCl)
30 mg and 60 mg tablets

DESCRIPTION

CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+)-cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem hydrochloride for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given, a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina. CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIONS and ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS).

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%), AV block (1.1%). In addition, the following events were reported infrequently (less than 1%) with the order of presentation corresponding to the relative frequency of occurrence.

Cardiovascular:	Flushing, arrhythmia, hypotension, bradycardia, palpitations, congestive heart failure, syncope.
Nervous System:	Paresthesia, nervousness, somnolence, tremor, insomnia, hallucinations, and amnesia.
Gastrointestinal:	Constipation, dyspepsia, diarrhea, vomiting, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH.
Dermatologic:	Pruritus, petechiae, urticaria, photosensitivity.
Other:	Polyuria, nocturia.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: erythema multiforme; leukopenia; and extreme elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been limited. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral/LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. Although individual patients may respond to any dosage level, the average optimum dosage range appears to be 180 to 240 mg/day. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

Cardizem 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1771-49). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1772-49). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

Issued 4/1/84

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Benefits diuretics cannot offer... Once-daily INDERAL LA (propranolol hydrochloride) with its smooth 24-hour control of blood pressure provides a high degree of patient acceptance without potassium problems, plus the cardiovascular benefits of the world's leading beta blocker.

Experience no other beta blocker can match... Once-daily INDERAL LA delivers the proven performance and safety profile of INDERAL tablets—confirmed by millions of patients during 16 years of clinical use. INDERAL LA should not be used in congestive heart failure, sinus bradycardia, heart block greater than first degree, or bronchial asthma.

Start with 80 mg once daily... Dosage may be increased to 120 mg or 160 mg once daily as needed to achieve additional control. Please see next page for further details and brief summary of prescribing information.

ONCE-DAILY

INDERAL LA

(PROPRANOLOL HCl) LONG-ACTING CAPSULES

Just once each day for initial therapy in hypertension.

[illegible]

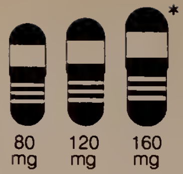
Ayerst

Just once each day for initial therapy in HYPERTENSION.

ONCE-DAILY

INDERAL® LA

(PROPRANOLOL HCl) LONG ACTING CAPSULES



BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)*
INDERAL® LA brand of propranolol hydrochloride **(Long Acting Capsules)**
DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.
CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and [illegible]ewhat variable. INDERAL has been shown to cause a small increase in serum potassi[illegible] concentration when use[illegible] the treatment of hypertensive patients

In angina pectoris, propranolol generally reduces th[illegible]n re[illegible]t any given level of effort by blocking the catecholamine[illegible] inc[illegible] in the h[illegible] rate, systolic blood pressure, and the velocity and extent of [illegible]rdial [illegible] th[illegible]nolol may increase oxygen requirements by increasing left [illegible]ular f[illegible] length, [illegible]stolic pressure and systolic ejection period The net phy[illegible]rene[illegible]ade is usually advantageous and is manifested dur[illegible]ercis[illegible]e[illegible]f [illegible]nd increased work capacity

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-[illegible] or anesthetic-like membrane action which affects th[illegible]c a[illegible]nti[illegible]ig[illegible]cance of the membrane action in the treatment of [illegible]ythm[illegible] is [illegible]cert[illegible]

The mechanism of the antimigraine effect of pr[illegible]anolol [illegible] n[illegible]lished. B[illegible]-adrenergic receptors have been demonstrated in [illegible] pial ves[illegible]

Beta receptor blockade can be useful in con[illegible]ns in [illegible] bec[illegible] path[illegible]r functional changes, sympathetic activity is detri[illegible]u[illegible]so situations in which sympathetic stimulation is vital. F[illegible] example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.
INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary
CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma; 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL
WARNINGS. CARDIAC FAILURE Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible)

> IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors

Just once each day...

MAJOR SURGERY. The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA. Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker In one case this resulted after an initial dose of 5 mg propranolol.
PRECAUTIONS. *General:* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in [illegible] rats [illegible] empl[illegible]oses [illegible] 150 mg/kg/day, there was no evidence of significant [illegible]lated tumorigenic effects at any of the dosage levels [illegible] duc[illegible]dies [illegible]mals [illegible] not show any impairment of fertility that was attrib[illegible] to th[illegible]

[illegible]ncy: [illegible]ncy Cat[illegible]ry C. INDERAL has been shown to be embryotoxic in ani[illegible]ies a[illegible]s [illegible]er than the maximum recommended human dose

Th[illegible] are n[illegible]eq[illegible]d w[illegible]rolled studies in pregnant women INDERAL should be used during p[illegible]gnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mot[illegible]s: INDERAL is excreted in human milk Caution should be exercised when [illegible]DERAL [illegible] adm[illegible]ste[illegible] a [illegible]rsing w[illegible]an

Pe[illegible]ric [illegible]ely a[illegible]ctive[illegible]ss in children have not been established
[illegible]VE[illegible]SE R[illegible]ACTIONS. [illegible] ad[illegible]se effects have been mild and transient and have [illegible]rely [illegible]quired [illegible] of [illegible]

C[illegible]iovas[illegible] [illegible]brady[illegible]dia [illegible]gestive heart failure; intensification of AV block, hypo-[illegible]nsio[illegible] thr[illegible]urpura; arterial insufficiency, usually of the [illegible]aynaud type.

Central Nervous System [illegible]headedness, mental depression manifested by insomnia, lassitude, weakness, fatigue, [illegible]eversible mental depression progressing to catatonia, visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.
DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved The usual maintenance dosage is 120 to 160 mg once daily In some instances a dosage of 640 mg may be required The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks

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If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

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MEETINGS AND LECTURES

The New York State Journal of Medicine *cannot guarantee publication of meetings and lectures unless the information is submitted at least two months prior to the event.*

NOVEMBER 1984

AROUND THE STATE

MANHATTAN

Nov 1–3. **Update on Genito-Urinary Oncology.** *Nov 17.* **Third Annual Meeting of the New York State Society of Critical Care Medicine.** Memorial Sloan-Kettering Cancer Center. Info: CME Conference Planning Office, C-180, 1275 York Ave, New York, NY 10021. Tel: (212) 794-6754.

Nov 2. **New Ambulatory Medical & Surgical Techniques Applicable to Venous Disorders.** *Nov 3.* **Intraperitoneal Endoscopy-Peritoneoscopy-Laparoscopy.** *Nov 12–16.* **Surgery of the Paranasal Sinuses.** *Nov 27.* **Medical Ethics: The Jewish Point of View.** *Nov 28.* **Advances in Perinatology.** *Nov 30.* **Eighth Annual Brookdale Medical Conference on Aging: Controversies in Geriatric Medicine III.** Mount Sinai Medical Center. Info: Page & William Black Post-Graduate School of Medicine, One Gustave L. Levy Place, New York, NY 10029. Tel: (212) 650-6737.

Nov 5, 12, 19, 26. **How to Write a Scientific Paper.** Beth Israel Medical Center. Info: Post-Graduate Medical Education Office, Beth Israel Medical Center, 10 Nathan D. Perlman Place, New York, NY 10003. Tel: (212) 420-2849.

Nov 7–9. **Innovative Cancer Chemotherapy for Tomorrow: Chemotherapy Foundation Symposium VI.** 20 Cat 1 credits. Barbizon Plaza Hotel. Info: Page & William Black Post-Graduate School of Medicine, One Gustave L. Levy Place, New York, NY 10029. Tel: (212) 650-6737.

Nov 8–10. **Medicolegal Aspects of Cardiac and Pulmonary Disease and Injury.** Essex House. Info: American Society of Law & Medicine, 765 Commonwealth Ave, Boston, MA, 02215. Tel: (617) 262-4990.

Nov 13. **Training the Physiatrist of Tomorrow.** 1 Cat 1 credit. St. Vincent's Hospital & Medical Center. Info: Samuel S. Sverdlik, MD, Director of Department of Rehabilitation Medicine, St. Vincent's Hospital & Medical Center of New York, 153 W. 11th St, New York, NY 10011. Tel: (212) 790-8506.

Nov 14. **Diabetes Teaching Day.** Cabrini Medical Center. Info: Dr Ira Laufer, Director of Diabetes, Department of Medicine, Cabrini Medical Center, 227 E. 19th Street, New York, NY 10003. Tel: (212) 725-6000 or (212) 944-7899.

Nov 14–17. **Rhinoplasty: A State of the Art Symposium.** 21 Cat 1 credits. Waldorf Astoria Hotel. Info: Francine Leinhardt, Coordinator, Plastic Surgery Clinic, Manhattan Eye, Ear and Throat Hospital, 210 E. 64th St, New York, NY 10021. Tel: (212) 838-9200, ext 2776.

Nov 17–18. **Third Annual Conference of the Center for the Study of Anorexia and Bulimia.** Barbizon Plaza Hotel. Info: Center for the Study of Anorexia and Bulimia, 1 West 91st St, New York, NY 10024. Tel: (212) 595-3449.

Nov 17–18. **New Technologies in Urology.** 15½ Cat 1 credits. *Nov 28–30.* **Pitfalls in Surgery.** 19 Cat 1 credits. Info: NYU Medical Center Post-Graduate Medical School, 550 First Ave, New York, NY. Tel: (212) 340-5295.

Nov 28. **Update Neurology.** New York Hospital. Info: Lila A. Wallis, MD, CME, The Association of Practicing Physicians of the New York Hospital, 1300 York Ave, Room D115, New York NY 10021. Tel: (212) 737-4444 or (212) 472-6119.

Nov 30 & Dec 1. **Neuropeptides: Implications for Neurologic and Psychiatric Diseases.** Hotel Roosevelt. Info: Association for Research in Nervous & Mental Disease, Inc, Bernard Cohen, MD, Mt. Sinai School of Medicine, 1 Gustave Levy Place, Room 21-74, New York, NY 10029. Tel: (212) 348-8133.

BRONX

Nov 1. **Pathology of the Aging.** 2 Cat 1 credits. *Nov 8.* **Advances in Beta Blockage.** 2 Cat 1 credits. *Nov 15.* **Kidney Stones.** 2 Cat 1 credits. Info: Westchester Square Hospital, in collaboration

Continued on p 12A

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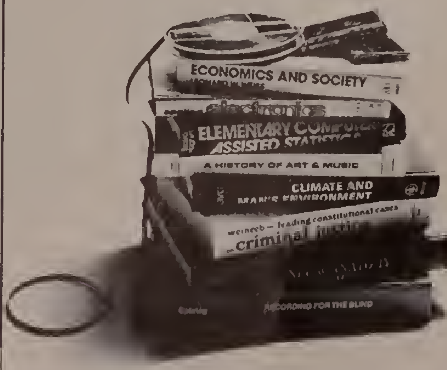

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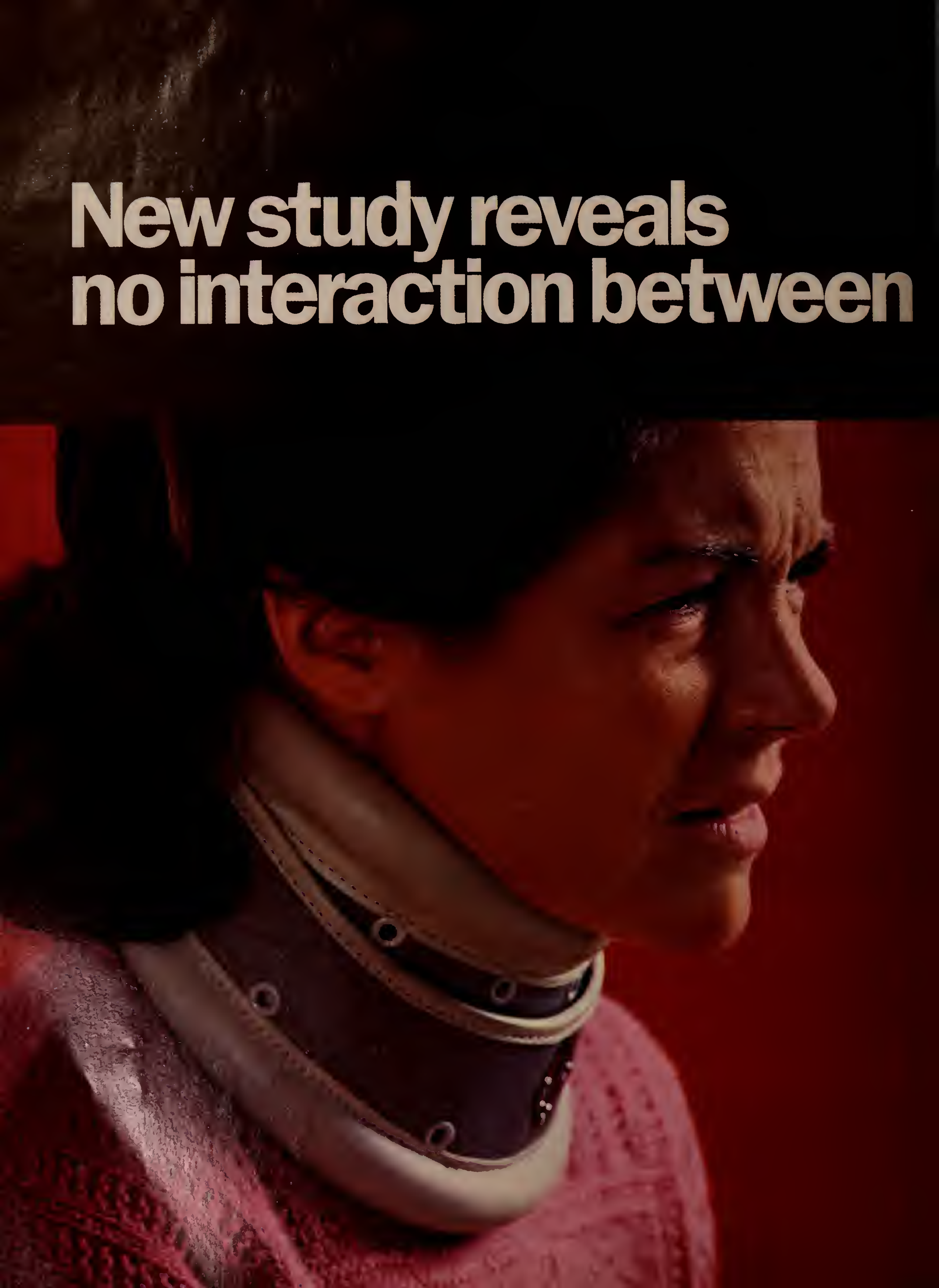
New study reveals
no interaction between

Ativan® (lorazepam) and Darvon® (propoxyphene HCl) Ⓒ

In a study evaluating the influence of propoxyphene coadministration on the pharmacokinetics of the oxidatively metabolized benzodiazepines Xanax® (alprazolam) Ⓒ and Valium® (diazepam) Ⓒ, and a benzodiazepine metabolized by conjugation, Ativan® (lorazepam), the following results were reported:

with Xanax, propoxyphene caused a large and highly significant prolongation of half-life and impairment of total metabolic clearance.[1]

in the case of Valium, propoxyphene produced a small but not statistically significant impairment of clearance.[1]

propoxyphene had no apparent effect on the distribution, half-life or clearance of Ativan.[1]

In this randomized crossover study, eight healthy male and female volunteers received single oral doses of alprazolam (1 mg), six received single IV doses of diazepam (10 mg), and five received single IV doses of lorazepam (2 mg), once in a drug-free control state and again during coadministration of propoxyphene (65 mg q6h). Consistent with previous findings, this study evidences that Ativan does not interact with drugs that undergo oxidative metabolism.[2-5] In contrast to most other benzodiazepines, Ativan does not compete for the cytochrome P-450 enzyme system.

The clinical implications of the pharmacokinetic interaction, or non-interaction, of propoxyphene with benzodiazepines are not established by this study. Even without a pharmacokinetic interaction, propoxyphene and benzodiazepines share central depressant properties and therefore should be coadministered with suitable caution. A concurrent pharmacokinetic interaction indicates a need for even further caution. Coadministration of propoxyphene and alprazolam, for example, would produce not only the expected pharmacodynamic interaction, but also whatever additional central depressant effect would be produced by the elevated steady-state plasma concentrations of alprazolam due to its impaired clearance.

Caution should also be observed when propoxyphene is prescribed for patients who use alcohol to excess.

References
1. Abernethy DR, Greenblatt DJ, Shader RI: Data on file, Wyeth Laboratories.
2. Patwardhan RV, Yarborough GW, Desmond PV, et al: Gastroenterology *79*:912-916, 1980.
3. Abernethy DR, Greenblatt DJ, Divoll M, et al: Psychopharmacology *80*:275-278, 1983.
4. Abernethy DR, Greenblatt DJ, Divoll M, et al: N Engl J Med *306*:791-792, 1982.
5. Ochs HR, Greenblatt DJ, Abernethy DR: Data on file, Wyeth Laboratories.

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Ativan® for (lorazepam) Ⓒ Anxiety

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DISTINCTIVE DESIGN 0.5, 1.0 and 2.0 mg

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection USP. Usefulness of dialysis has not been determined.

Ativan® Ⓒ IV
for (lorazepam)
Anxiety

DOSAGE: Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.

HOW SUPPLIED: 0.5, 1.0 and 2.0mg tablets.

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with Albert Einstein College of Medicine/Montefiore Hospital & Medical Center, Conference Room, 2475 St. Raymond Ave, Bronx, NY 10461. Tel: (212) 430-7300.

BROOKLYN

Nov 4. **Current Advances in Ischemic Heart Disease.** Kings County Medical Society. Info: Miss Hazel Spadafora, Executive Director, 1313 Bedford Ave, Brooklyn, NY 11216. Tel: (212) 467-9000.

NASSAU

Nov 8. **Allergy and Immunology Teaching Day.** East Meadow. 5 Cat 1 credits. Info: Nathan S. Weiss, MD, Department of Pediatrics, Nassau County Medical Center, 2201 Hempstead Turnpike, East Meadow, NY 11554. Tel: (516) 542-2177.

QUEENS

Nov 2. **Current Clinical Psychopharmacology.** 7 Cat 1 credits. Sloman-Lowenstein Auditorium, LIJ-Hillside Medical Center. Info: Ann J. Boehme, CME Coordinator, LIJ-Hillside Medical Center, New Hyde Park, NY 11042. Tel: (212) 470-2114.

DUTCHESS

Nov 8. **Medical Management of the Diabetic Patient.** 1 Cat 1 credit. Rhinebeck. Info: Vivian Cadbury, Northern Dutchess Hospital, Rhinebeck, NY 12572. Tel: (914) 876-3001.

ERIE

Nov 12–13. **Update on Anesthesia Management of Obstetrical Patients.** 4 Cat 1 credits. Children's Hospital, Buffalo. Info: Kurt G. Becker, NYS Society of Anesthesiologists, Inc, 30 E. 42nd St, Ste. 1501, New York, NY 10017. Tel: (212) 867-7140.

Nov 29. **Biomolecular Events Underlying Cancer.** 5 Cat 1 credits. Buffalo. Info: Gayle Bersani, RN, Department of Education, Roswell Park Memorial Institute, 666 Elm St, Buffalo, NY 14263. Tel: (716) 845-2339.

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NEW YORK STATE
JOURNAL OF MEDICINE

October 1984 • Volume 84, Number 10

COMMENTARIES

Measles—past, present, and future

The last 20 years have seen a dramatic change in the incidence of measles. Whereas in the early 1960s, just prior to the licensure of the measles vaccines, there were about five million cases of measles per year, in 1983 there were only 1,436 cases reported.[1] Thanks to a safe and efficacious vaccine, at least 4,840 deaths have been prevented, 16,100 cases of mental retardation averted, and much suffering avoided. In short, the benefit to the American people has been enormous; a recent cost-benefit analysis estimated a total saving of $4.5 billion.[2] This is a great triumph for both science and public health.

However, the chances for maintaining this success are less clear. The date of measles elimination, originally hoped for by the Centers for Disease Control as October 1, 1982, remains elusive. There has been a 46.2% increase in the number of cases in the first five months of 1984 compared to 1983.[3] With the continued high degree of surveillance, immunization laws, and diligent public health professionals, how can this be? The answer lies in an understanding of the epidemiology of measles before and after the vaccine.

Prior to the vaccine, approximately 10.6% of the total population was susceptible to measles.[4] Importantly, this susceptible pool consisted mainly of children less than 10 years of age. In fact, over 90% of children over age 10 and at least 99% of young adults over age 20 were naturally immunized.[2,5] When the vaccination initiative began, the pool of susceptible children began to acquire artificial immunity. The inevitable result was a large drop in total population susceptibility. With 100% of adults naturally immunized and the many children who were artificially immunized, the population susceptibility dropped to approximately 3.1%, or about half that necessary to sustain endemicity.[4,6] Thus, measles disappeared from most states and communities.

A problem occurs because the vaccination program for measles does not do as good a job at eliminating susceptible individuals as does Mother Nature. If measles fades out in most communities, all immunity must be derived by artificial means. Currently, the standard is about 95% seroconversion in those vaccinated, with about 97% of children being vaccinated by the time they enter kindergarten, for a total protection rate of 92% (.95 × .97 = .92). It should be noted that the vaccination rate of 97% is a recent phenomenon, and has actually been less for most of the elimination program, thereby further reducing vaccine coverage. It takes no great stretch of the imagination to appreciate that if this were to continue into the 21st century, many more people would be susceptible, and they would be distributed among all age groups; with advancing age, morbidity and mortality subsequent to measles infection are more likely. A recent modeling study showed that this prolongation of susceptibility results in perhaps as many as 220,000 more people susceptible to measles each year.[3]

What is the solution to this ever growing number of susceptible individuals? First, their susceptibility would be of no consequence if measles disappeared in the rest of the world—no virus, no disease—as with smallpox. Unfortunately, this is not likely to occur in the near future. Measles elimination is less of a priority and logistically more difficult in the developing world. Even in developed countries, the progress in measles elimination is relatively slow. Thus, the chance of importing the disease, already a significant problem, must be minimized with vaccination certificate requirements. Next, work must continue to improve both vaccine efficacy and immunization rates in children. Maintaining effective vaccine coverage above 95% would go a long way toward curbing the rising susceptibility rate.

Are there any lessons to be learned from the measles experience that could be applied to widespread vaccination programs for ubiquitous childhood illnesses? Have we made a mistake with measles? The answer to the first question is yes, there are lessons to be learned, but no, the measles elimination initiative has not been a mistake. The savings in terms of lives and suffering due to measles and its complications can never be considered an error. To abandon the effort now would be to ignore the challenge of tomorrow—to preserve today's gains for future generations. Although the balance of nature has been altered, this change must be viewed only as another obstacle to ensuring a society free of measles. The lesson is that the attempt at elimination of a disease in the short term may pose unforeseen problems in the long run, and that tampering with the ecological balance in some other circumstance, such as a similar attempt to eliminate varicella—a virtually benign disease of childhood—may create greater problems than are solved.

DAVID LEVY, MD
Department of Family Medicine
Tuxedo Memorial Hospital
Tuxedo Park, NY 10987

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Risks and benefits of pulmonary artery catheters

Bedside pulmonary artery catheterization using flow-directed balloon-tipped catheters to measure intrapulmonary pressures, cardiac output, and mixed venous oxygen content has gained widespread acceptance for the hemodynamic management of critically ill patients in intensive care units.[1] Nonetheless, the procedure may result in life-threatening complications.[2–5] These include heart block, ventricular tachycardia and fibrillation, catheter-related sepsis, pulmonary infarction, and injury to the pulmonary valve.

The most feared complication of pulmonary artery catheters is rupture of the pulmonary artery.[6–10] This catastrophe results in massive hemoptysis which is usually fatal. Pulmonary hypertension, advanced age, and the use of anticoagulants have been reported to predispose patients to this complication. Technical factors related to the catheter itself may contribute: balloon overinflation, flushing the catheter while wedged, manipulating or advancing the catheter while wedged, or the presence of intraventricular catheter loops which permit distal migration of the catheter.

In this issue of the *Journal*, Brandstetter et al[11] report another technical factor that may have contributed to fatal pulmonary artery rupture. They document the presence of a distal kink in the catheter as an incidental finding on a lateral chest roentgenogram. It is speculated that the kinked catheter snagged and lacerated the pulmonary artery when removal of the catheter was attempted. The origin of the kink is uncertain; it may have resulted from damage to the catheter tip at the time of its insertion.

Bedside pulmonary artery catheterization and monitoring is expensive and occasionally lethal, as this case demonstrates. Catheter-related mortality in seriously ill patients may be as high as 4%.[12] Therefore, it is important to ask whether a favorable risk-benefit ratio supporting the use of Swan-Ganz catheters in critically ill patients has been demonstrated. Clearly, data obtained by means of pulmonary artery catheterization are superior to clinical evaluation for differentiating cardiac edema from pulmonary edema caused by increased permeability, and for assessing the intravascular volume. Fein et al[12] showed that for patients in intensive care with pulmonary edema, the clinical diagnosis of congestive heart failure based on history and physical findings was incorrect 38% of the time. Measurement of the pulmonary capillary wedge pressure led to a more accurate diagnosis. The authors postulated that the inaccuracy of the clinical diagnosis of congestive heart failure occurs because many physical findings such as rales and edema are ubiquitous in critically ill patients with multiple organ failure. Also, background noise, airway secretions, and noise from mechanical ventilation in an intensive care unit obscure auscultatory findings. Connors et al[13] found similar results: physicians at all levels of training could estimate pulmonary capillary wedge pressure accurately only 42% of the time. They also found that in 30 of 62 patients data derived from the pulmonary artery catheter resulted in a significant change in clinical management, such as initiation of diuretic therapy or fluid administration.

Although pulmonary artery catheters provide helpful data, it should be emphasized that neither these studies, nor any other prospective controlled study, has shown that the probability of patient survival is improved by their use. Many critically ill patients ultimately die of the underlying disease, whether fluid therapy is managed by trial-and-error or by monitoring pulmonary artery pressure and cardiac output. Conversely, many survive regardless of the method used. If 4% of critically ill patients who are treated with catheters die from complications, more must be saved by the catheter for the odds to favor catheter use. This has never been shown.

It is likely that increased scrutiny of the financial cost of intensive care procedures will soon create additional pressures to evaluate the risks and benefits of bedside pulmonary artery catheterization. Meanwhile, meticulous attention to technique in catheter insertion, maintenance, and withdrawal are essential to prevent avoidable catheter-related deaths. Observation of a structural peculiarity of the catheter tip should be added to the list of factors that alert physicians to the possibility of impending pulmonary artery rupture, and the preventive measures suggested by Brandstetter et al should be considered.

JEAN E. RINALDO, MD
Division of Pulmonary Medicine
University of Pittsburgh
School of Medicine
Pittsburgh, PA 15261

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Non-surgical methods of kidney stone removal

In few areas of medical practice has change come about as fast as in the surgical treatment of kidney and ureteral stones. In less than three years the standard of treatment has shifted from open surgery to endourologic or endoscopic methods of stone removal.

An important characteristic of these techniques is that they can be adapted from practical techniques developed in academic medical centers to private urologic practice with equal results. The paper by Peartree et al[1] in this issue of the *Journal* confirms the successful translation of this method to a community hospital setting.

The success rate reported by Peartree and colleagues (95%) is similar to the success rates reported in other medical centers and in private practice. One of the keys to success, particularly initial success, is patient selection, and the results presented in this series are in large measure attributable to the authors' careful patient selection. As a result, their "learning curve" is much less pronounced than in other experiences.

In expert hands, 98% of surgical calculi are removable by percutaneous techniques. This includes staghorn calculi, calculi in any portion of the kidney, and ureteral stones. In general, the easiest stones to remove are those 1.5 cm or less in size and located in the renal pelvis. Even large staghorn calculi can be removed, unless there are so many dendritic extensions into the calices that total removal is not possible or practical. The addition of the flexible nephroscope with a flexible electrohydraulic lithotrite permits access to all areas of the collecting system. Even stones in the ureter can be removed by basket techniques, often via direct vision with a rigid ultrasonic lithotrite, or by manipulating the flexible instrument down the ureter.

It must be emphasized that the most important aspect of percutaneous stone removal is accurate guide wire placement; in most cases this is performed by a radiologist. Indeed, the most successful results occur when urologists and radiologists work together on these cases.

When all goes well, patients treated by endourologic methods leave the hospital sooner than surgical patients and are less disabled by the procedure. Patients can return to moderate activity a week after the procedure and can participate in more vigorous activity in two weeks. If a patient leaves the hospital on the fourth day after the procedure, the cost saving will be 25% to 30% over a standard open surgical procedure in which the patient would have stayed seven to eight days.

The authors correctly point out that a metabolic work-up is essential for such patients. A complete evaluation will often reveal a treatable cause of stone formation, and it is usually possible to prevent recurrent stone formation.

There is a risk of arteriovenous fistula formation; an incidence of less than 1% has been reported in large series.[2,3] In an unpublished study of more than 1,000 cases, Segura and colleagues identified six such fistulas. This is the most significant sequela, and it should be treated by arteriography and embolization of the peripheral vessel. This treatment is curative and minimizes loss of functional renal parenchyma.

There are no apparent long-term complications of these procedures. Marberger and colleagues and Segura and colleagues reported no increased risk of stone formation with follow-up of four years and one year, respectively, at the American Urological Association meeting in May 1984.

The development of endourologic procedures, the increased use of ureterorenoscopy, and the advent of extracorporeal shock wave lithotripsy will make open surgical procedures an uncommon operation reserved for the occasional stone too large or too sequestered to be removed by any other method.

JOSEPH W. SEGURA, MD
Department of Urology
Mayo Clinic
Rochester, MN 55905

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Radionuclides, regulations, and rationality

Radioactive isotopes have become essential to modern medicine. Johnson and Abernathy[1] estimated that between six and seven million imaging procedures are performed annually in the United States. The 1980 report of the National Academy of Science Committee on Biological Effects of Ionizing Radiations (BEIR III) stated that 10 million to 12 million such examinations were done each year.[2] Ten times that number of radioimmunoassays are performed annually.

Physicians understand the benefits of these non-invasive, physiologically oriented imaging procedures. The reduced risks of these tests over others enable evaluation of cardiac performance, hepatobiliary and renal function, and pulmonary perfusion, for example, in seriously ill patients for whom more invasive procedures are not recommended. The high sensitivity of radionuclide imaging permits accurate surveys for metastatic cancer and hidden infections. New developments in labeling monoclonal antibodies with radiation promise improved detection and therapy of malignant tumors and other diseases.

In addition to their diagnostic usefulness, radioisotopes are required for research efforts in physiology, pathology, and pharmacology. Such research has led to a better understanding of neurotransmitters and may lead to the development of methods for treating conditions such as schizophrenia and Alzheimer's disease. Radioisotopes are also used to study cellular proliferation in leukemia and solid tumors.

This research requires the use of tracers such as tritium (^3H) or carbon 14 (^{14}C), both weak beta particle emitters that can be traced only after solutions of digested tissue or blood specimens are mixed with a scintillation fluid, usually an organic solvent. The amount of radioactivity that escapes from the fluid is negligible and does not constitute a hazard unless ingested or inhaled, in which case the chemical toxicity of the fluid is a far greater hazard.

No one is more aware that radioactivity has risks than physicians who use these radiotracers every day. But they are also aware that the benefits of these procedures far outweigh potential risks. Trained in the proper handling and applications of radioactivity, they need not fear it as something magical or threatening.

The ongoing brouhaha, fomented by the media, concerning radiation and anything with the term "nuclear" in its name, has caused general public confusion concerning the problem of waste disposal. The subject of safe disposal of low level radioactive wastes generated by the biomedical and energy industries, which should be a straightforward matter, has become entangled with fears of nuclear weapons and the economic or political debates about nuclear power. It appears useful for some politicians and various appointed officials to pander to these fears and confusions by issuing public statements that obstruct efforts to provide safe, efficient, and cost effective disposal methods. Using statements made by the more rabid anti-nuclear forces, such as "there is no safe level of radiation," they undermine the credibility of the scientific community and medical sources and thereby defeat attempts to alleviate public fear by increased education. They may be exposing the populace to much more serious risks than those they attribute to radioactivity.

There is a risk to everything in life. In some matters, the greatest risk is doing nothing. A case in point is the recent collaboration between several New York City Council members and Health Department officials to prevent local incineration of certain types of low level waste by Rockefeller University, and to use public testimony and the press to undermine the reputation of that university in the process. The level of radioactivity of these biomedical wastes is so low that the United States Nuclear Regulatory Commission (NRC) has determined that they can be disposed of without regard to their radioactivity. The director of laboratory safety at Rockefeller University, Edward L. Gershey, PHD, has stated that the amount of radioactivity is minute and that the problem is political rather than scientific.[3] We believe his assessment is correct. On the other hand, Andrew

Stein, borough president of Manhattan and a candidate for Congress, claims that "exposures to even low levels of radiation can be deadly." [4] This is a scientifically meaningless statement.

NRC regulations permit disposal of materials without regard to their radioactivity when concentrations are below 0.05 microcuries per gram or milliliter of ^3H or ^{14}C.[5] This standard is accepted by 49 states, including New York State. Rhode Island, while not permitting incineration, does permit disposal as toxic waste at these levels. New York City stands alone in rejecting these standards.

The New York City Department of Health has estimated the radiation dose to an individual from incineration of radioactive wastes produced by the city's large medical research institutions as 0.52 mrem/yr to bone from 975 mCi of ^{14}C and 0.68 mrem/yr whole body dose from 18,638 mCi of ^3H to an individual, based on inhalation of tritiated water and ^{14}C carbon dioxide 40 meters from the incinerator stacks.[5] These exposures are less than 1% of natural background. Extrapolating down to this level from BEIR III estimates would mean 0.01 to 0.002 additional deaths from cancer over the lifetime of one million people exposed to this dose annually. This can be compared to a natural lifetime cancer mortality rate of about 167,000 persons in this size population.

By congressional mandate, states are required to be responsible for and have developed a method of disposal for low level radioactive waste generated within their borders by January 1, 1986. Around the country, state governments are discussing this issue and are deciding whether to enter into regional pacts for that purpose or to develop intrastate options. These efforts are taking longer than needed because of the atmosphere of fear that surrounds the issue. The risk of doing nothing to facilitate timely and affordable disposal options is that certain areas of biomedical research will not be possible, and efficacious clinical tests will be priced out of existence. Physicians must make their voices heard, educate their patients about the need for and safety of these materials and methods, and require that elected and appointed officials act in the public interest.

HAROLD L. ATKINS, MD
Professor of Radiology
SUNY at Stony Brook
Stony Brook, NY 11794

LETTY G. LUTZKER, MD
Associate Director of Radiology/
Nuclear Medicine
Woodhull Hospital
760 Broadway
Brooklyn, NY 11206

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The commissioner of the New York City Department of Health, David Sencer, MD, was invited to contribute a commentary, but did not reply. —*Editor*

Reflections on the recent hospital strike

During the recent strike against voluntary hospitals and nursing homes in the metropolitan area, by District 1199 of the Retail, Wholesale, and Department Store Union, a physician who plodded through many days of work in a hospital records department had much time for reflection.

In the end, what did the strike accomplish? Having lost 13.15% of their annual pre-strike wages during the seven-week walkout, during the next two years the workers will gain an increase of 15.25% (5% of pre-strike wages during the first year, plus an additional 5.25% the second year). The resulting subtraction yields a 2.1% gain overall. Irrespective of cost-conscious pronouncements of elected government officials during the strike, the public is well aware that ultimately, by one mechanism or another, it will pay the bill for any wage increases. The fact that the money may not pass through the hands of the state government makes little difference.

How is it possible for a hospital system to continue at 80 to 90% capacity in the absence of 40,000 to 50,000 of its employees? Even granting the presence of part-time substitutes and limitation of some services, why was there an impression in at least one hospital of better overall performance in many hospital services during the strike? Comments to the effect that "Patients used to complain before the strike; now they seem happier" were not infrequent. Did this reflect a genuine improvement in services, or simply the willingness of patients to endure inevitable hardship? Was the interior of the building truly "so much cleaner?" Were the remaining hospital personnel truly "more courteous and helpful?" If so, how long could such improvements have continued if the strike lasted indefinitely? Serious but unpopular questions of this kind might be raised about the level of productivity of hospital personnel before and after the strike; but it is unlikely that their answers will be pursued.

The union would be wise to rethink its role. Should not it place a greater value upon itself, not granting membership to just anyone who signs an application form and pays dues? Should union membership and benefits initially be extended to applicants on a provisional basis only, with final membership conditional on worker performance during an adequate probationary period? Can unions revive their role in society to assist workers who are initially forced into work that tends to stifle hope and latent ambition? Many hospital positions, which on the surface seem menial, are essential to the welfare of patients, particularly when related to routine clerical tasks, food services, waste removal, and cleanliness. Perhaps both union and management should attack the problems experienced in such jobs by limiting the time spent doing a specific job by any one worker, review of worker performance, and providing counselling for a worker if performance is graded less than satisfactory. Could such jobs be shared among personnel, even among those who demonstrate ambition to advance beyond the rote? Could such jobs be used as steps toward advancement, as part of educational efforts that would move the employee toward more personally satisfying goals? For those who prefer no change in job status irrespective of the type of work, should not their performance and level of satisfaction be monitored? All jobs involve rote, some more than others; but rigid job descriptions, initially meant to protect the worker, have become traps and excuses for the frustrated employee. For others, they have become excuses for not performing needed tasks, all at additional expense to the public. The union must rethink its raison d'être or continue to be the whipping-boy of the media and the public. The small union risks being swallowed up by larger, more powerful, and more aggressive unions on the one hand, or gradually being swept aside by the inevitable pressures of financial constraints and corporate aggressiveness. The strike has proven once again that anyone can endure almost anything in the short term—it is the long term that requires a reorientation of thinking.

Present governmental policies tend to penalize the hospital system in the name of "cost-containment," yet at the same time quietly pass the ultimate costs of deteriorating hospital facilities and modernization efforts onto the next generation of taxpayers and governing officials. A truly forward-looking governor and commissioner of health would be initiating, as well as publicizing, the results of pilot research projects to improve hospital cost accounting, medical information storage and retrieval, food services, inter-hospital information exchange and cooperation in clinical care, and other vital hospital functions. Hospital fiscal requirements and the impact of improved technologies will have to be faced sooner or later and by all the parties involved.

Can the voluntary, non-profit hospitals learn a lasting lesson from this strike, which will help them to compete with the growing corporate-hospital organizations? Will the union continue to maintain an adversary position, or should it carefully rethink its policies, aware that corporate hospitals could be much tougher adversaries in the future? Will everything revert to "normal" after the strike, in spite of increases in wages? The painful experiences of the strike will be wasted unless hospital boards and managers, union leaders, and elected officials consider the future from the perspective of better patient care, rather than merely cost containment, workers' rights, or management's prerogatives.

Physicians are inexperienced in judging what goes on in the workplace, or what workers must endure. Despite the repetitive routines of their own profession, physicians usually have sufficient respite and adequate rewards that make their daily tasks endurable. Not so for many others in the work force. But it is only when a physician shares the burdens of others that he is forced to give thought to problems that commonly fail to reach his everyday awareness.

LETTERS TO THE EDITOR

Address correspondence to Editor, New York State Journal of Medicine, *420 Lakeville Road, Lake Success, NY 11042. Letters should be typed double-spaced and include the signature, academic degree, professional affiliation, and address of each author. Preference is given to letters not exceeding 450 words, and every effort will be made to assure prompt publication. All letters are personally acknowledged by the Editor.*

Offshore medical schools

TO THE EDITOR: This is sent to congratulate the *Journal* on its July 1984 issue. The subject was timely, the matter complicated, and the issues consequential. They were dealt with well. Dr Imperato, Deputy Editor, is to be commended.

My particular interest stems from long-past experience in the recruitment of physicians, when I was New York State Commissioner of Mental Hygiene. As director of Marcy State Hospital, I was involved in planning programs for residents and senior students from abroad.

It is hoped that you have excited concern—and action—on the part of the medical profession for the benefit of the patient and the student. I believe that the Board of Regents will listen to the state medical society.

Perhaps your next topic might be physician maldistribution, a complex issue that also requires prompt, effective attention.

No doubt, many readers have commented favorably about the new organization, format, and style of the *Journal*.

NEWTON BIGELOW, MD
Ives Road
Marcy, NY 13403

Responses to review of *How to Write and Publish a Scientific Paper*

TO THE EDITOR: In Lois DeBakey's review of my book *How to Write and Publish a Scientific Paper* (*NY State J Med* 1984; 84:146-147), she finds it "surprising" that the book has been favorably reviewed in other journals (hundreds, actually); she, on the other hand, is able to perceive that the book is nothing more than "a gallimaufry of bits and pieces" by a "nescient neophyte." The apparent reason for DeBakey's position is that the book is "not original." She then goes on to say that it is not original because a portion of it "was reproduced verbatim as it appeared in the copyrighted *The Scientific Journal: Editorial Policies and Practices* (1976) by Lois DeBakey.

I have no problem with the first part of that. DeBakey is certainly entitled to her opinions.

In the second part, however, we are not dealing with opinion but with fact. Did I, in fact, use material from DeBakey's book without appropriate attribution? The answer is no. On page 83 of the second edition of *How to Write and Publish a Scientific Paper* (or page 75 of the first edition, which has exactly the same wording) appears the following: "I believe that these questions are well answered in 'Guidelines for Reviewers, American Society for Microbiology," (ASM) which is reprinted at the end of this chapter. The ASM guidelines are patterned after policies recommended by a committee of the Council of Biology Editors (CBE) some years ago. The same policies, or variations of them, have been adopted by many journals. Some of these policies were discussed at some length by DeBakey[18], a former Chairman of the CBE committee."

It can be added that the quoted ASM guidelines were published in the 1974 edition of the *ASM Handbook for Journal Editors*, and that the ASM guidelines were patterned after the "Guidelines for Reviewers" originally published in the April 1970 issue of the *CBE Newsletter*.

ROBERT A. DAY
ISI Press
3501 Market Street
Philadelphia, PA 19104

TO THE EDITOR: Lois DeBakey's excoriation of Robert Day's book *How to Write and Publish a Scientific Paper* is undeserved and unfortunate. While holding herself up as a paragon of professional rectitude, DeBakey has accused a distinguished colleague of one of the most serious breaches of ethical conduct. She says, "Are scientific authors to follow his [Day's] suit and violate a cardinal ethical principle of scientific exposition and scholarship? In his first edition (1979), much of the 'Guidelines for Reviewers' was reproduced verbatim as it appeared in the copyrighted *The Scientific Journal: Editorial Policies and Practices* (1976) [by DeBakey]; yet no footnote acknowledged that source."

Actually, the first edition of Day's book contains, verbatim and with proper attribution, the "Guidelines for Reviewers" published by the American Society for Microbiology (ASM) in 1974 and distributed to all ASM journal editors and editorial board members. These guidelines were, for the most part, taken from recommendations by the Council of Biology Editors (CBE) as published in the April 1970 *CBE Newsletter*. There is absolutely no reason why Day should cite DeBakey's 1976 book, since she apparently took, verbatim, guidelines that had already been published elsewhere. To accuse Day of plagiarism is a calumny that cannot go unchallenged.

DeBakey also chides Day for failing to cite her book in his second edition, where she sees only a "rearrangement" of her own work. She says, "The rearrangement of that material in the second edition does not relieve the author's obligation to cite the copyrighted source. . . ." She asks rhetorically, "Does Day understand his own words when he writes '. . . to use the work of others without appropriate attribution, is the type of breach in scientific ethics that is regarded as unforgivable by one's peers'?" The clear implication is that the "rearrangement" was a ruse to avoid an "obligation." This implication is wrong.

The "rearrangement" represents modifications of the ASM guidelines that Day properly asked us to provide to update his book. It reflects current ASM practices, not the sinister motives of an unscrupulous author.

By implication, DeBakey has also accused ASM of failing to cite her book properly, since Day reprinted the ASM guidelines, with attribution, in their entirety in his second edition. Because of the chronology, any such implication is obviously nonsense.

What I find most vexing about the review is that DeBakey makes a few points worth consideration—the rigid use of tense, the definition of a scientific paper, and the definition of valid publication, for example. Unfortunately, these points are vitiated by a bitter and abusive attack that cannot possibly serve the interest of your readers.

WALTER G. PETER III
Director of Publications
American Society for Microbiology
1913 I Street, NW
Washington, DC 20006

In reply: My book review, which was carefully prepared, critically previewed, fully documented, accurate, and honest, stands on its merit. Day's misrepresentation of my text, by his merging of a general statement I made about the lack of originality with a more specific statement, suggests that he would profit from a rereading of the review, this time carefully.

Peter presumes to put thoughts in my mind and words in my pen, and he is way off base on both counts. The reader should, for example, substitute "inference" where Peter writes "implication"; one would think a director of publications would know the difference. For Peter to label as "a bitter and abusive attack" an honest review concurred in by leading authorities is, at the least, unconscionable and, at the most, far more serious. Without free and candid criticism, moreover, the entire scientific and scholarly endeavor would collapse, and the advancement of knowledge would suffer gravely. I will not dignify by a response Peter's *ad hominem* remarks and his invidious and benighted characterizations—expressed with more passion than prudence—but merely invite readers to contrast his language, tone, and documentation with those of my review.

LOIS DeBAKEY, PhD
Professor of Scientific Communication
Baylor College of Medicine
One Baylor Plaza
Houston, Texas 77030

The foregoing correspondence was sent for comment to several individuals, two of whom submitted their letters for publication.

TO THE EDITOR: In reading the letters by Robert Day and Walter Peter commenting on Lois DeBakey's review of Day's book *How to Write and Publish a Scientific Paper*, I feel compelled to plunge my oar into these tempestuous waters.

Lois DeBakey needs no defense of her preeminent position as defender of integrity and advocate of literacy in American medical letters. To those of us who know Lois, she represents the conscience of medical scientific journalism.

The fundamental principle that Day violated was failure to observe appropriate attribution, especially when complete paragraphs were borrowed virtually verbatim. The crowning bit of poor judgment was to poach on the preserve of Lois DeBakey. The only analogy that comes to mind would be not only to steal a car, but to steal the police chief's car.

The DeBakey review of the Day book was penetrating, forthright, and in conformity with the facts as they are known to all who are familiar with the chronology of events. The *ad hominem* attack by Peter was unworthy of a professional editor and did a grave injustice to one of the great medical writers and editors of our time.

I do not know Robert Day or Walter Peter, but I do know Lois DeBakey; Day and Peter are way out of line and certainly far out of their league.

ROBERT H. MOSER, MD
Executive Vice President
American College of Physicians
4200 Pine Street
Philadelphia, PA 19104

TO THE EDITOR: Messrs Day and Peter confuse this issue by ingeniously distorting the historical facts. As founder and first chairman of the Committee on Editorial Policy of the Council of Biology Editors (CBE), which formulated the "Guidelines for Reviewers" referred to, perhaps I can dispel the confusion. This committee, formed in the late 1960s, studied the guidelines for reviewers of several journals before issuing a recommended set of guidelines in the uncopyrighted *CBE News* in 1970. The intention was to stimulate editors to re-examine their current guidelines and, if they approved of the committee's set, to adopt them. It was unforeseen and unintended that a professional society would adopt and publish these guidelines as though they were the society's own unaided invention, but that, according to Mr Peter, is what the American Society for Microbiology (ASM) did. Mr Day was managing editor of the ASM's journals at the time.

The CBE committee worked on other aspects of editorial policy and eventually published the outcome of its deliberations, including the guidelines for reviewers, in *The Scientific Journal: Editorial Policies and Practices* (1976), edited by Dr Lois DeBakey. Dr DeBakey was a member of the committee from its inception, succeeded me as its chairman in 1971, and published the book on behalf of the committee members with their full agreement and collaboration. Thus, the correct attribution of the guidelines would have been to the "CBE committee on editorial policy, originally published in 1970 and presented in book form by DeBakey in 1976; they have been adopted by many journals, including those of the American Society for Microbiology, whose slightly re-worded version is reproduced here." Mr Peter's account of the chronology is disingenuous, and Mr Day's text misleading. The error was brought to the publisher's attention after publication of the first edition but was left uncorrected in the second.

This legalistic quibbling over publication dates may unfortunately distract readers' attention from the much more important criticisms of Mr Day's book in Dr DeBakey's review, in which she exposes by direct citation the author's lines of argument and mode of expression. I heartily concur with another reviewer's opinion, cited (without attribution) by Mr Day in his own preface to the second edition: the book is a mixture of the good and the original; what is good is not original, and what is original is not good. Mr Day's approach is epitomized by his statement in the preface to the first edition, and repeated in the second, that he would "view the book as a success . . . if it makes me rich and famous." Dr DeBakey could have selected other examples of Mr Day's borrowing of others' less aggressively marketed books, including two of my own, but confined herself to one with which she had personal experience. Mr Peter's intemperate personal attack on Dr DeBakey is particularly uncalled for (she has never "held herself up as a paragon of moral rectitude," although as a matter of fact she *is* one) and reflects badly on the American Society for Microbiology, which I presume approved the wording of his letter.

F. PETER WOODFORD, PhD
1 Akenside Road
London NW3 5B6
England

Diagnosis and treatment of pelvic lymphoceles in the renal transplant recipient

Alan M. Lessner, md, Neil Lempert, md, Donna M. Pietrocola, md,
Richard T. MacDowell, md, Carl E. Haisch, md, James Cerilli, md

ABSTRACT **Five cases of lymphoceles after renal transplantation are described. We attribute this low incidence (1%) of lymphoceles to careful ligation of all pelvic lymphatic vessels at the time of surgery. The signs and symptoms of pelvic lymphatic accumulations are variable and may appear as an asymptomatic abdominal mass or renal allograft rejection. The diagnostic value of ultrasound, radioisotopic renal flow scan, and computerized axial tomography is stressed. The benefits and complications of percutaneous aspiration of lymphoceles are described. Internal drainage of uninfected lymphoceles is the recommended surgical procedure.**

(NY State J Med 1984; 84:491–494)

Introduction

Lymphoceles are a recognized complication of renal transplantation. The reported incidence varies from 0.6% to 18%.[1,2] While most lymphoceles are asymptomatic, some patients have fever, leukocytosis, a rising serum creatinine level, or swollen legs. The routine use of ultrasonograms and computed axial tomographic (CAT) scans has improved the detection of both small and asymptomatic lymphatic fluid collections.

Much controversy exists over the origin and pathophysiologic appearance of lymphoceles. Investigators hypothesize that they may arise from improperly ligated lymphatic vessels surrounding the external and internal iliac vessels.[3,4] Others believe that the donor kidney is the source of lymph drainage, either from pericapsular or hilar lymphatic vessels.[5] The incidence of lymphoceles in renal transplant patients is approximately 1% at this institution. The diagnosis and management of five cases will be presented and discussed in this article.

Methods and Results

From August 1969 to December 1983, 387 renal allograft procedures were performed at the Albany Medical College. At the time of transplantation, meticulous care was taken to clip or ligate all obvious lymphatic tissue over the iliac vessels. Frequently, the nodal tissue was removed entirely, and all branches were ligated. In five recipients, or approximately 1.2%, perirenal lymphoceles developed (Table I). This represents the absolute incidence of fluid collections detected clinically with the aid of radiographic techniques. In one patient, the lymphocele was noted to be infected, which altered the course of surgical treatment.

The patient with a suspected lymphocele should undergo a physical examination as well as blood cell counts, chemistry studies, and a screen for clotting disorders. The principal diagnostic techniques have been ultrasonography, radioisotopic renal flow test and scan, and intravenous pyelogram with tomographic scans. The renal flow scan is useful in detecting a urinoma or fistula but is not helpful in demonstrating a lymphocele. Intravenous pyelography, however, can not only demonstrate leakage of contrast material but also provides information about masses that may be visualized with carefully obtained tomographic scans. When necessary, a CAT scan is obtained to facilitate the diagnosis. Sterile aspiration of the fluid collection is then performed under fluoroscopic control. At the time of aspiration, a catheter is inserted into the most dependent portion of the lymphocele to facilitate complete drainage. Samples of the fluid are sent for blood cell count, chemistry studies, and cultures. Two ampules of indigo carmine are then given intravenously. When the dye has appeared in the urine the fluid from the lymphocele is checked for the presence of indigo carmine. Chemistry study results of the fluid collection are compared with the blood chemistry study results to help differentiate lymphocele fluid from urine. If the fluid is found to be infected, external drainage is instituted. If the fluid is not infected, the patient is discharged and checked periodically for reaccumulation of the lymphocele. If the lymphocele recurs, the patient is readmitted and internal drainage of the lymphocele is undertaken. This procedure is carried out at the time of laparotomy through a midline peritoneal incision. The lymphocele is initially aspirated to ascertain its location. It is then completely evacuated, and a large margin of cyst wall is excised to allow complete drainage of the lymphocele into the peritoneal cavity.

Case 1. A 24-year-old man had end-stage renal disease because of chronic glomerulonephritis. After bilateral nephrectomy, he received a kidney from a living relative in 1974; the kidney was rejected within two months. Ultimately, a transplant nephrectomy was required. On January 26, 1976, he received a two-antigen–matched kidney from a cadaver and experienced minimal rejection. On December 5, 1976, he was readmitted for studies of an asymptomatic palpable pelvic and abdominal mass. The physical examination was unremarkable except for a noticeable swelling of the abdomen over the site of the transplanted kidney. The patient's creatinine level was stable at 1.3 mg/dL, and his urine output was within normal limits. His WBC count was 50,000 cells/mm^3, and a bone marrow biopsy demonstrated a chronic granulocytic leukemic process. An abdominal ultrasonogram revealed a cystic mass 10 cm in diameter posterior to the bladder and medial to the kidney. The cyst was aspirated on December 10, and 600 mL of clear fluid was obtained. Culture of the fluid was negative. A cell count of the fluid demonstrated 240 cells/mm^3 with a differential count of 90% lymphocytes and 10% monocytes; the fluid creatinine level was 1.2 mg/dL. The patient remained afebrile after the procedure, with stable renal function and a creatinine

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From the Department of Surgery, Albany Medical College, Albany, NY.
Address correspondence to Dr Lempert, Director, Transplantation Division, Department of Surgery, Albany Medical College, Albany, NY 12208.

TABLE I. Clinical Data

Case	Initial Appearance (No. days after transplant)	Fever	Palpable Mass	Leg Edema	Deterioration of Renal Function	Symptoms Present	No. Days from Internal Percutaneous Aspiration to Accumulation	Surgical Procedure	Serum Creatinine Level (mg/dL) Before/After Surgical Procedure	Results
1	315	N*	Y	N	N	N	27	Internal drainage	1.3/1.3	Good
2	431	Y	Y	Y	Y	Y	2	External drainage	1.5/0.8	Good
3	78	N	Y	N	Y	Y	17	Internal drainage	1.7/1.3	Good
4	395	N	Y	N	N	Y	49	Internal drainage	0.9/0.8	Good
5	31	N	Y	Y	Y	Y	16	Internal drainage	1.7/1.3	Good

* N, No; Y, Yes.

level of 1.3 mg/dL. On March 8, 1977, he was readmitted for recurrence of the lymphocele. An internal drainage procedure was performed by creating a wide opening between the lymphocele and the peritoneal cavity. The lymphocele did not recur.

Case 2. A 59-year-old woman with insulin-dependent diabetes received a two-antigen–matched kidney on June 30, 1977, and had a mild rejection. She was subsequently treated for a recurrent urinary tract infection and a fungal empyema. In September 1978, she complained of abdominal pain over the kidney graft site and had mild dysuria. Her urine output was adequate, and her serum creatinine level was 1.5 mg/dL. A physical examination elicited marked right lower quadrant tenderness over the graft site. A temperature of 102°C developed, and a urine culture revealed greater than 10^5 Gram negative rods. An ultrasonogram and renal flow scan showed a lucency approximately 15 cm in greatest diameter at the inferior pole of the transplanted kidney. The mass displaced the bladder superiorly and to the left of the pelvis. The intravenous pyelogram did not reveal hydronephrosis. On September 12, 1978, she underwent a cystogram, which showed leftward displacement of the bladder. Under fluoroscopic control, approximately 600 mL of fluid was evacuated by percutaneous aspiration. A Gram's stain and culture of the fluid showed Gram negative rods that were identified as *Klebsiella pneumoniae* and were sensitive to tobramycin. Indigo carmine dye was injected intravenously and did not enter the lymphocele. The lymphocele was then drained externally, and three Penrose drains and a large mushroom catheter were sewn into place in the cavity. After several days of antibiotics and drainage, the patient's temperature returned to normal and her serum creatinine level dropped to 0.8 mg/dL. Delayed primary closure of the skin and fascia was performed when the lymphocele cleared of infection and drainage had ceased.

Case 3. A 53-year-old man received a two-antigen–matched kidney from a living relative in September 1981. The patient did well, with only minimal rejection until December 1, 1981, when he was admitted because of shortness of breath, abdominal distension, and pain in the groin. On December 1, 1981, the patient underwent a percutaneous tap of the abdominal mass, which yielded lymph. The creatinine level was stable at 1.7 mg/dL. A radioisotope renal flow scan disclosed flow to the kidney, with reduced activity medial to the graft, compressing and deforming the urinary bladder. An intravenous pyelogram showed hydronephrosis. Because of recurrence of the lymphocele, abdominal exploration was undertaken on December 18, 1981. An internal drainage procedure was constructed to empty the lymphocele into the peritoneal cavity. The patient tolerated the procedure well, and his lymphocele did not recur. After surgery, the patient's creatinine level dropped from 1.7 mg/dL to 1.3 mg/dL.

Case 4. A 27-year-old woman received a one-antigen–matched kidney from a cadaver in May 1982 after two years of chronic renal failure, peritoneal dialysis, and hemodialysis. Her postoperative course was unremarkable until February 1983, when she complained of pain in the right lower quadrant and abdominal distension. A physical examination confirmed the presence of a lower abdominal mass. Ultrasonography delineated a perirenal fluid collection and moderate hydronephrosis (Fig 1). A CAT scan demonstrated a large fluid collection surrounding the transplanted kidney (Fig 2). In June 1983, she underwent percutaneous aspiration of the lymphocele. Intravenous indigo carmine was not detected in the 1,500 mL of aspirated fluid, which precluded the presence of a urinoma. In August 1983, the lymphocele recurred and was drained by the intraperitoneal route. The patient was discharged from the hospital with excellent kidney function and has not had a recurrence of the lymphocele.

Case 5. A 31-year-old woman received a two-antigen–matched kidney from a living relative in December 1983. She reentered the hospital with a symptomatic abdominal mass and a swollen extremity on the same side as the transplant. An ultrasonogram and a CAT scan (Fig 3) defined a massive pelvic fluid collection. Initial aspiration showed a lymphocele; the cultured fluid was negative. Despite complete evacuation at the time of aspiration, the fluid reaccumulated within two weeks. On January 16, 1984, she underwent successful intraperitonealization of the lymphocele with excision of a portion of the lymphatic sac.

DISCUSSION

A lymphocele is a collection of lymph in a nonepithelialized cavity lined with fibromembranous tissue.[6] Symptoms usually occur within six months from the time of transplant; however, cases have been reported as early as 18 days or as late as 17 months after surgery.[7]

The signs and symptoms of a patient with a lymphocele vary considerably. A number of patients remain asymptomatic, and their lymphoceles are detected only when routine ultrasonography is performed. The symptomatic patient may appear with a palpable pelvic or abdominal mass, abdominal pain, fever, ipsilateral ankle or leg edema, hypertension, urinary frequency, or persistent incisional drainage overlying the renal transplant.[7] The patient also may show signs of decreasing renal function, including a rising serum creatinine level and diminished urine output. The diagnosis is not always readily apparent, since these signs and symptoms often represent graft rejection.[8,9]

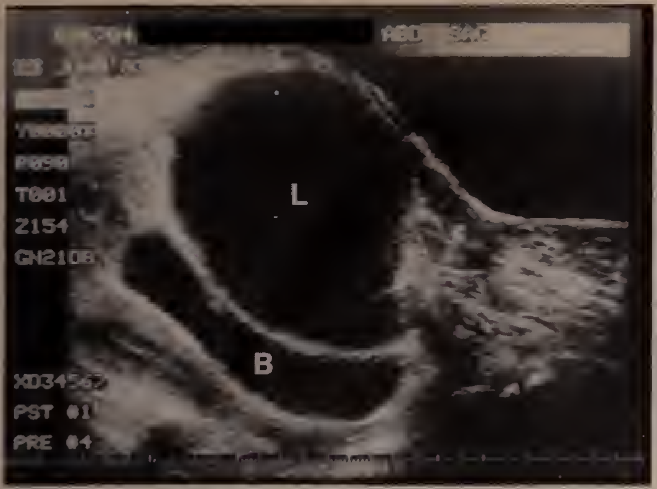

FIGURE 1. Case 4, pelvic ultrasound, B mode. Large anterior fluid collection (L) is shown compressing bladder (B) posteriorly.

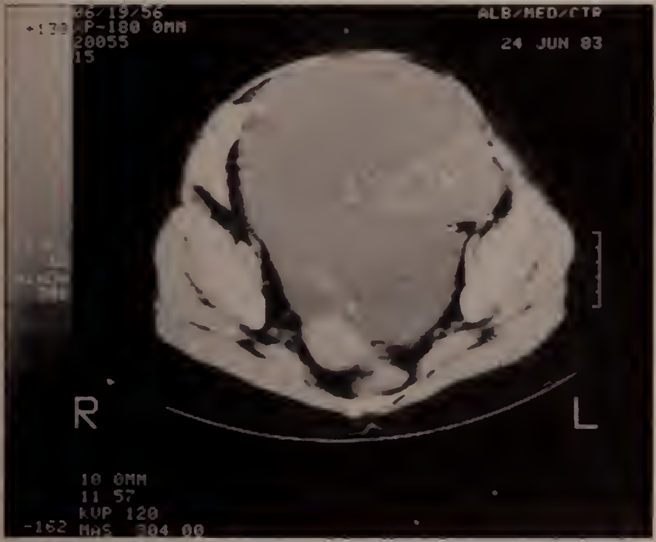

FIGURE 2. Case 4, pelvic computed axial tomographic scan with oral contrast. Large fluid collection (L) fills most of lower pelvis and surrounds transplanted kidney (K).

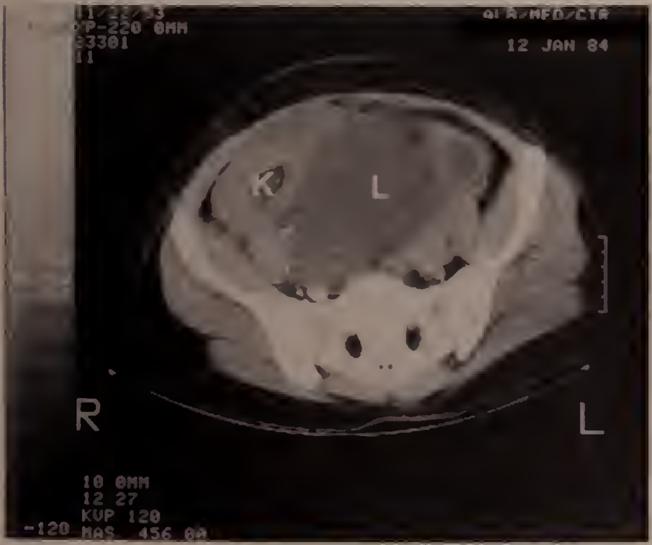

FIGURE 3. Case 5, computed axial tomographic scan with contrast showing large fluid collection (L) contiguous with transplanted kidney (K).

Many factors contribute to the formation of a lymphocele. Most authors agree that inadequate ligation of the pelvic lymphatic vessels that overlie the internal and external iliac vessels serve as a source of lymphatic accumulation.[3,4] Lymphangiography has demonstrated extravasation of dye from the common and external iliac lymphatic networks after renal transplantation.[10-12] A low incidence of lymphoceles has been reported at institutions where meticulous care is taken to ligate the perivascular lymphatic vessels.[3] Other more subtle causes of lymphoceles include leakage of lymph from the transplanted kidney,[10] the presence of an arteriovenous fistula on the same side as the transplant,[7] or decapsulation of the transplanted kidney.[5] The use of steroids has been reported to increase lymphatic flow, and anticoagulants may delay closure of lymphatic vessels severed during surgery.[12]

Radiographic studies are the prime techniques for diagnosis of the patient with a lymphocele. The most sensitive and specific radiographic method is lymphangiography. The drawbacks of this technique, however, are the invasive nature of the test, pain on injection, allergy to the dye, potential extravasation of the dye, and a mortality rate of approximately 1 in 1,000.[10] Roentgenograms, cystograms, and intravenous pyelography with tomograms may show the presence of a mass that displaces pelvic structures such as the ureter, bladder, or the transplanted kidney. Ultrasonography is a sensitive and noninvasive method of detecting pelvic masses.[13] Unfortunately, this technique has a low specificity for fluids and cannot distinguish an early hematoma, abscess, urinoma, or other fluid-filled mass from a lymphocele. Both intravenous indigo carmine dye or intravenous pyelography can be helpful in ruling out a urinoma. A urinoma is suspected if dye is visualized in the fluid-filled sac. At this institution, the use of ultrasonography in conjunction with renal flow scans and CAT scans has been extremely successful in differentiating intrinsic from extrinsic causes of diminished renal function. One may become suspicious of a mass if the renal pelvis is obstructed or a cold area signifying bladder compression is evident. A urinoma may be visualized on the renal flow study if a concentration of technetium is visualized in both the bladder and an extrarenal location. In our opinion, lymphangiography is rarely warranted, because ultrasonography is quite sensitive in detecting small to moderate-sized fluid collections. In patients who received both lymphangiography and ultrasonography, the latter has been reported to detail a more accurate estimation of the size of the fluid collection.[10]

We believe the use of percutaneous aspiration should be considered as a diagnostic tool rather than a therapeutic procedure. The aspirate can be sent for cell count, chemistry studies, and microbiologic culture. Many small asymptomatic lymphoceles spontaneously regress and may be managed by close observation. Usually, moderate to large lymphoceles will reaccumulate fluid after aspiration and eventually may reach or surpass their original proportions. Multiple-needle aspirations, however, should be avoided. The complications of repeated percutaneous aspiration include bacterial contamination and subsequent fistula formation, hematoma formation, and unintended puncture of a vital structure such as the ureter.[14]

If the lymphocele is sterile, internal marsupialization is the treatment of choice, as it minimizes the risk of postsurgical infection. Using a transperitoneal approach, the anterior wall of the lymphocele is removed, creating a window for drainage between the cyst and the peritoneal cavity.[4,15]

Currently, we do not recommend aspiration or surgical treatment for the small and asymptomatic lymphocele that does not interfere with renal allograft function. External drainage is the recommended treatment for infected lymphoceles. The patient is given appropriate systemic antibiotics, and the lymphocele is markedly decompressed.

Acknowledgments. This work was supported by the James Hilton Manning and Emma Austin Manning Foundation.

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Percutaneous removal of kidney stones

ROBERT J. PEARTREE, MD, RONALD A. RUOTOLO, MD, FUAD J. KHURI, MD,
JOHN R. VALVO, MD, ARTHUR J. SEGAL, MD

ABSTRACT Two recent developments in the field of urology are beginning to revolutionize surgery for kidney and ureteral stones. Percutaneous nephrolithotomy and ureterorenoscopy now provide the urologic surgeon with the ability to view and operate throughout the entire urinary tract within a controlled, closed system. These two techniques have inspired the term "endourology." Using percutaneous ultrasonic lithotripsy, we have successfully removed 49 stones from 53 renal units. There were three failures, for a success rate of 92%. There were no serious complications, and most patients were able to resume their preoperative activities within 10 days after discharge from the hospital. The main advantages of reduced morbidity, shorter hospitalization, and overall increased cost efficiency threaten to make open surgery for many kidney stones obsolete.

(NY State J Med 1984; 84:494–497)

INTRODUCTION

Open, conventional renal surgery for urolithiasis often requires a large flank incision with considerable postoperative discomfort to the patient. Goodwin et al[1] were the first to show, in 1955, that the kidney could be accessed by percutaneous means. Further refinements in endoscopic equipment and radiographic technique allowed the urologic surgeon to view the intrarenal anatomy and extract small stones.[2,3] The use of an ultrasound probe, pioneered by Kurth et al[4] and Alken et al[5] allowed disintegration and removal of stones larger than the nephrostomy channel.

To date, most large series have been confined to major academic centers.[6–8] These centers have proved this approach to be reliable, safe, and cost efficient. We therefore commenced a preliminary study in September 1983 to determine the feasibility and logistics of incorporating percutaneous lithotripsy in a community setting. We report our experience with the first 51 patients.

PATIENTS AND METHODS

Fifty-one patients, 30 men and 21 women, were considered candidates for percutaneous renal stone removal. The only contraindication for this procedure was a bleeding diathesis. Their ages ranged from 18 to 84 years. Twelve patients had had prior surgery on the affected side. Multiple stones were identified in six patients and bilateral stones in two patients.

The procedure was performed in one or two stages and, with a few modifications, was similar to that reported by Segura et al.[9] The first stage, performed in the radiology suite, consists of insertion of a percutaneous nephrostomy tube using fluoroscopic control and local anesthesia. This is followed, usually within 24 hours, by percutaneous manipulation within the operating room under sterile conditions. Two patients underwent the one-stage procedure in which everything was performed under general anesthesia in the operating room.

A needle catheter assembly is placed into the calculus-con-

From the Rochester General Hospital Professional Building (Drs Peartree, Ruotolo, Khuri, and Valvo), and the Department of Radiology (Dr Segal), Rochester General Hospital.

Address correspondence to Dr Peartree, Suite 304, 1445 Portland Ave, Rochester, NY 14621.

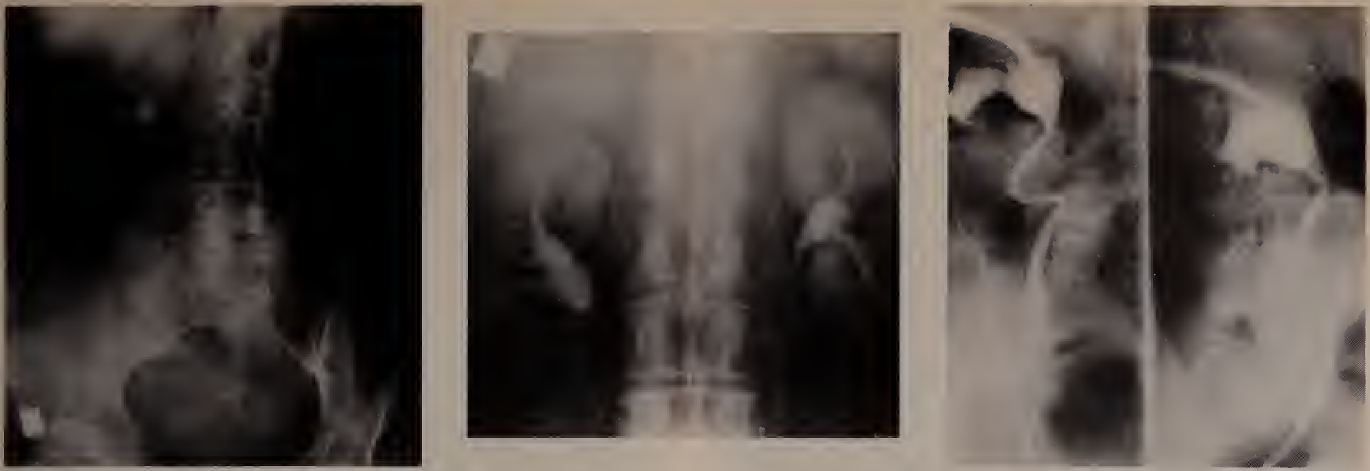

FIGURE 1. Left, 2-cm calculus in right renal pelvis of 65-year-old woman; Center, intravenous pyelogram showing nondilated collecting system; Right, postoperative nephrogram with absence of calculus and patent ureter.

taining calix, usually the lower or middle calix. For larger systems, we prefer intravenous contrast medium administration. For smaller and, particularly, nonobstructed systems, we prefer the retrograde catheter technique. The indwelling retrograde catheter allows a contrast medium to be injected during insertion.

A Lunderquist-Ring guide wire is used to advance the initial catheter, usually about 5 to 6 French units. This is followed by progressive dilation to at least 8 units, and ideally 12, depending on the patient's level of comfort. If possible, this catheter is placed in the ureter; however, in some patients with ureteropelvic junction obstructions or an impacted calculus at the ureteropelvic junction, the catheter is left in the intrarenal collecting system.

Under general anesthesia, a Foley bladder catheter is inserted, and the patient is placed in the prone position with the involved flank slightly elevated. The patient is prepared and draped in the usual sterile fashion. Using fluoroscopic guidance, two Lunderquist-Ring torque guide wires are inserted through the nephrostomy catheter and directed into the bladder. The safety guide wire is taped away from the operative field. Fascial or telescoping metal dilators are then passed over the guide wire in succession up to 24 French units.

The passage and position of the dilators must be monitored carefully to avoid inadvertent injury to the renal pelvis, the ureteropelvic junction, or the ureter. The metal dilators are particularly useful in patients who have undergone prior renal surgery. The 24-French nephroscope with obturator is then passed over the initial guide wire into the renal pelvis. The obturator and guide wire are removed, and the working element and lens are secured into position. Normal saline solution warmed to body temperature is used as the irrigating solution, with a continuous low-pressure flow system. The operator inspects the renal pelvis under direct vision and identifies such landmarks as the medial aspect of the renal pelvis, the safety guide wire, the ureteropelvic junction, and the position of the calculus. Depending on the size of the calculus, the operator decides whether the calculus can be removed with stone forceps, graspers, or baskets, or whether ultrasonic lithotripsy will be required.

Calculi larger than 8 mm are best managed with ultrasonic disintegration and removal of small fragments (Fig 1). Most of the patients had renal pelvic calculi larger than 1 cm and therefore required at least partial ultrasonic disintegration. The ultrasonic wand is inserted through the nephroscope, and under direct vision, the tip of the wand is gently impacted onto the surface of the stone. Using a foot control, ultrasonic energy is transmitted down the wand into the stone. As the calculus begins to fragment, small pieces are suctioned through the continuous flow system and trapped in a vacuum satchel for analysis of the stone.

After removal of all fragments, a 20-French red rubber catheter is inserted down the nephroscope sheath; its position in the renal pelvis is checked with contrast medium, and the safety guide wire is removed. The catheter is connected to a continuous drainage system for 24 hours, and a nephrotomogram is performed (Fig 2). If all fragments have been removed and there is no ureteropelvic junction edema or extravasation, the nephrostomy opening is clamped and closed within 24 hours. The patient is usually discharged on the fourth or fifth hospital day.

RESULTS

Percutaneous removal of the stones was successful in 49 of 53 renal units, for a success rate of 92% (Table I). Forty-nine stones were removed in all. The stones were composed mainly of calcium oxalate, except in one patient, a quadriplegic, who had struvite stones. One patient had had a pyeloplasty 20 years earlier; a branched partial staghorn calculus was removed under a one-stage procedure.

There were two failures secondary to impacted ureteral calculi, and the other two failures were secondary to improper nephrostomy tube placement.

All patients were discharged within one week after percutaneous renal surgery, and the majority returned to their activities by the time of the first postoperative visit, usually within two weeks. The quadraplegic patient with infected stones was free of stones and infection four months following the procedure. There were no deaths and no subsequent open procedures. Total operating time ranged from one hour to four hours and 15 minutes. Operating time is dependent on the size of the calculus, its composition, the position and number of stones, and the degree of bleeding. Rapid dilation will result in some bleeding and clot formation; however, this has not been a serious problem in this series. The use of the flexible choledochonephroscope proved invaluable in removing a fragment that migrated into a calix during ultrasonic lithotripsy.

Complications occurred in six patients. In one patient, a retroperitoneal hematoma occurred that required a two-unit transfusion but subsequently resolved. The patient was discharged seven days after surgery. Two patients were noted to have intraoperative extravasation, indicating a leakage from the renal pelvis. Extravasation must be carefully monitored. If this exceeds 1 L, the procedure should be terminated. Using normal saline solution as the irrigant, no serious sequelae were noted by absorption of extravasated fluid. A hyponatremic syndrome has been reported with extravasation when glycine was used as the irrigant.[10] We have used warmed, normal saline solution exclusively and have not seen this problem. Four patients were identified as having residual fragments (3 mm and smaller) by plain

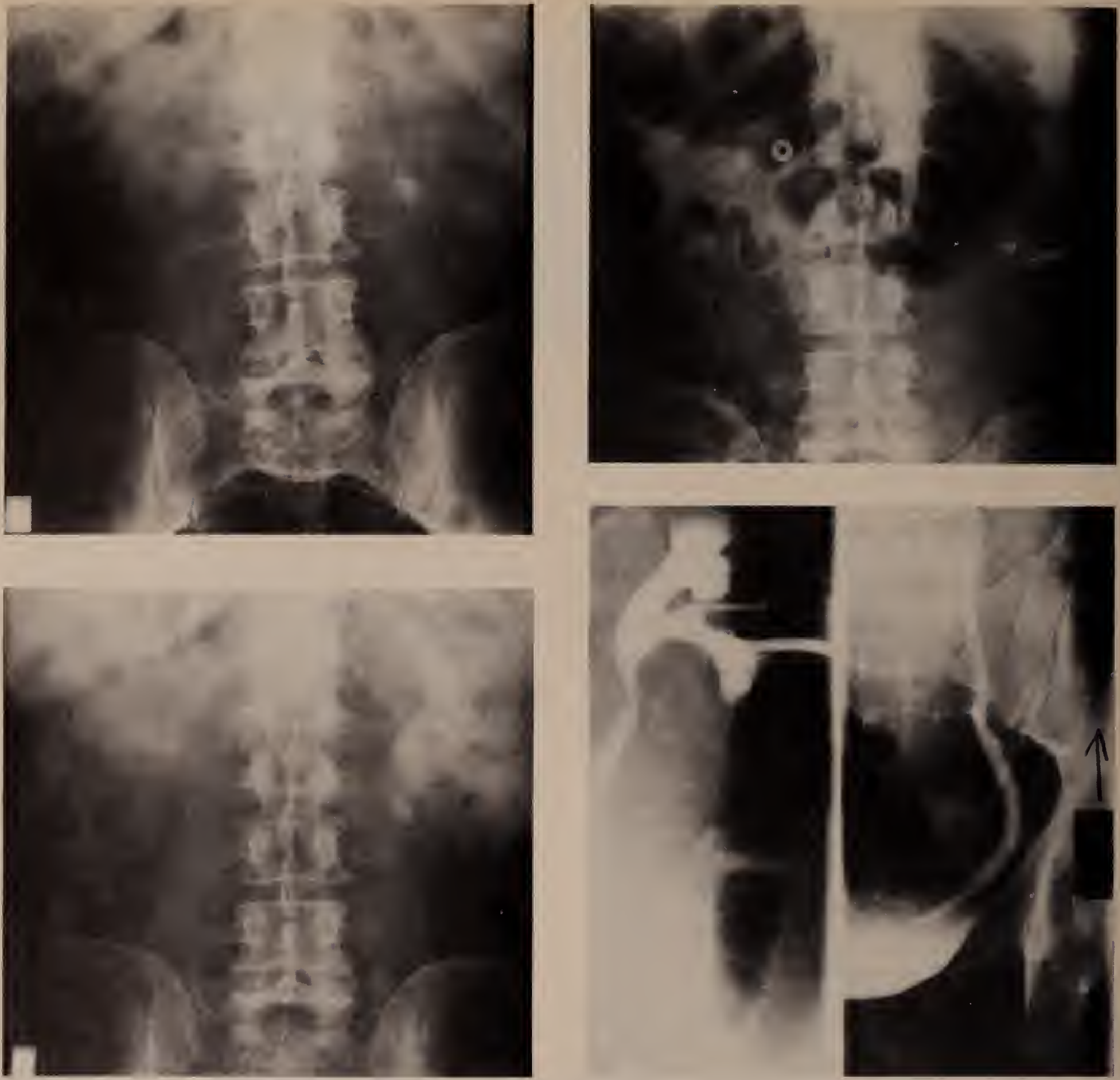

FIGURE 2. Top left, 8-cm calculus at left ureteropelvic junction in 53-year-old man; Bottom left, intravenous pyelogram showing hydronephrosis; Top right, postoperative scout film showing nephrostomy tube and no residual calculi; Bottom right, postoperative nephrotomogram reveals no extravasation and patent ureter.

nephrotomography after surgery. These were all passed spontaneously. Persistent drainage, secondary to ureteropelvic junction edema, resulted in prolonged nephrostomy drainage in two patients, which resolved within one week after discharge from the hospital.

Discussion

There is ample evidence in the literature and from our own experience that percutaneous lithotripsy can be performed safely on most patients who previously had required open, conventional surgery.

We have shown percutaneous lithotripsy to be an effective means of removing renal pelvic stones and some caliceal stones. The most difficult stones to remove are small caliceal stones in nondistended collecting systems. Nevertheless, with accurate nephrostomy catheter access, these may be grasped and removed without the need for lithotripsy. It is imperative to have the flexible choledochonephroscope available for all percutaneous stone manipulations.

The percutaneous approach offers several advantages to the urologist and the patient. These include easy access to the renal pelvis with minimal trauma and excellent vision of intrarenal anatomy. Symptomatic calculi not easily amenable to open surgery may be removed percutaneously. In addition, reduced morbidity, shorter hospitalization, and

TABLE I. Results in 51 Patients

Total renal units	53
Successful removal	49
Failures	4
Repeat procedures	6
Average hospital stay	5.7 days
Success rate	92%

earlier return to preoperative activities can be enjoyed by most patients.

The recurrence rate of metabolic stones is significant, regardless of the means of extraction. Therefore, the need for second or third surgical procedures is often seen. In this series, six patients had prior surgery on the affected side. The technical difficulty of open surgery increases with each recurrence. However, repeated percutaneous procedures should pose little difficulty. It must be noted that complete metabolic studies should be performed in cases of recurrent stone formation. The only absolute contraindication to percutaneous stone removal is in patients with bleeding diathesis. Other contraindications include hepatomegaly; splenomegaly; solitary kidney, caliceal or impacted ureteral calculi; extreme obesity; and unreasonable patient expectations.

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Rapidly progressive fulminating tuberculosis

VENKITA JAGADHA, MD, GITA RAMASWAMY, MD

ABSTRACT **Tuberculosis is recognized as a classic example of a disease with protean manifestations. With current advances in chemotherapy, tuberculosis is a curable disease. Although its incidence is on the decline, the disease has by no means been eradicated. Over the past few years, attention has been drawn to disseminated tuberculosis, which often evades diagnosis until autopsy. This study analyzes eight cases in which the primary cause of death is attributed to tuberculosis. In five of the eight cases, the disease was first recognized at autopsy. Failure of antemortem diagnosis could result in a serious source of infection in the community and points out that tuberculosis should be considered when dealing with obscure illnesses, even in apparently healthy individuals.**

(NY State J Med 1984; 84:497–501)

INTRODUCTION

During the past few years attention has been drawn to the problems in diagnosing disseminated tuberculosis. In the present discussion, we describe eight cases where the primary cause of death was attributable to tuberculosis; however, in five of the eight cases the disease was first recognized at autopsy. This study reaffirms the observations of several authors[1-10] that tuberculous disease is still prevalent in the community and stresses the importance of a high index of suspicion for tuberculous disease when dealing with obscure illnesses, even in otherwise apparently healthy individuals.

METHODS AND CASE REPORTS

The autopsy records of the Metropolitan Hospital Center for a seven-year period (1977–1983) were examined for cases of fulminant tuberculosis. During this period 1,038 autopsies were performed, of which there were 21 documented cases of tuberculosis with histologic test results as confirmation. The diagnostic criteria included the finding of fibrocaseous tuberculosis, tuberculous bronchopneumonia, or miliary lesions with histologic evidence of tuberculoid granulomas, and the demonstration of acid-fast bacilli by the Ziehl-Neelsen technique in selected cases. Of the 21 cases, in 14 the diagnosis of tuberculosis was first established at autopsy. In eight of the 21 cases death was attributable to tuberculosis; the clinical and autopsy data of this subset were reviewed. The clinical data are summarized in Table I, and the autopsy findings are presented in Table II.

Case 1. A 26-year-old man sought treatment for a painful swelling of the right knee of 10 days' duration. His temperature was 103°F. Physical examination revealed a red, swollen right knee joint with effusion; bilateral rhonchi; and moderate respiratory distress. The liver edge was 3 cm below the costal margin.

From the Department of Pathology, Metropolitan Hospital Center, New York Medical College, New York.

Address correspondence to Dr Jagadha, Department of Pathology, Division of Neuropathology, Toronto General Hospital, EC4-316, 101 College St, Toronto, Ontario M5G 1L7, Canada.

TABLE I. Summary of Clinical Data

	1	2	3	4	5	6	7	8
Age (years)	26	44	32	34	75	38	62	75
Sex, Race	male, hispanic	male, black	female, black	male, hispanic	female, white	female, white	female, black	male, white
Duration of illness (days)	22	14	49	31	29	3	17	22
Duration of hospital stay (days)	12	1	42	24	8	3	15	15
Family history of tuberculosis (TB)	—	—	—	—	—	+	—	—
Past history of TB	—	+	—	—	—	+	+	—
Other conditions	—	Diabetes mellitus alcoholism	Drug abuse 7 years prior to admission, alcoholism	—	—	Alcoholism	Diabetes mellitus, chronic renal failure	Diabetes mellitus
Complaints	Monoarticular arthritis (right knee), fever	Fever, cough, abdominal pain, vomiting, diarrhea	Fever, cough, vomiting, jaundice, amenorrhea	Fever, cough, pleuritic pain	Hoarseness of voice	Confusion, agitation	Fever, weakness	Fever, dyspnea
Physical examination	Right-knee arthritis with effusion, bilateral rhonchi, hepatomegaly	Coarse rales, bronchial breathing left lower lobe, right upper quadrant tenderness	Scleral icterus, diminished breath sounds, vocal fremitus, right base hepatomegaly	Puffiness of face, generalized edema, right-sided empyema	Negative	Bilateral rales	Pleural and pericardial effusion	Severe respiratory distress, scattered rhonchi
Laboratory data	Disseminated intravascular coagulation, elevated BUN and creatinine	Elevated BUN	—	—	Elevated LDH	—	Elevated BUN, creatinine, and uric acid, elevated liver function test, anemia	—
Sputum acid-fast bacilli smear	—	+	—	—	+	+	—	—
Chest radiograph	Consistent with acute respiratory disease	Bilateral diffuse pneumonia	Atelectasis, right lower lobe infiltrate, pleural effusion	Right-sided empyema	Active bilateral pulmonary TB	Diffuse alveolar and interstitial infiltrates	Right pleural effusion, pericardial effusion	Scattered interstitial infiltrates
Purified protein derivative	Negative	Negative	Negative	Negative	Positive	Not done	Not done	Not done
Clinical course	Developed disseminated intravascular coagulation and acute respiratory disease	Severe respiratory distress, hypotensive episodes	Severe respiratory distress, renal failure	Renal failure, hypotension, respiratory distress	Severe respiratory distress	Severe respiratory distress	Severe respiratory distress, hypotension	Respiratory distress, coma
Clinical impression	Right knee arthritis, acute respiratory disease, disseminated intravascular coagulation	TB pneumonia with acute respiratory disease	Right lower lobe pneumonia with pleural effusion, hepatomegaly	Nephrotic syndrome with renal failure, empyema	Pulmonary tuberculosis	Chronic alcoholism, bronchopneumonia (tuberculous)	Chronic renal failure	Cerebrovascular accident

TABLE II. Summary of Autopsy Findings

	1*	2	3	4	5	6*	7	8
Lungs	M TB, TB-bronchopneumonia, bilateral acute respiratory disease	M TB (bilateral)	M TB, TB-bronchopneumonia (bilateral)	TB Gr, TB bronchopneumonia (right lung)	Bilateral cavitary TB, TB GR, TB bronchopneumonia	Extensive TB GR	M TB (bilateral)	Bilateral TB bronchopneumonia with candidal superinfection
Pleura	—	M TB	—	TB Gr	—	—	M TB	—
Peritoneum	—	—	TB Gr in omentum peritoneum	TB Gr	—	—	—	—
Pericardium	—	—	—	—	—	—	M TB	—
Heart	—	—	—	—	—	TB Gr in myocardium	—	—
Liver	—	M TB	M TB	—	TB Gr	—	M TB	—
Spleen	M TB	M TB	—	TB Gr	—	—	M TB	—
Kidneys	M TB	M TB	M TB	Amyloidosis	TB Gr	—	M TB	—
Adrenals	M TB	—	—	—	—	—	—	—
Lymph nodes	M TB	—	M TB	—	—	—	M TB	TB Gr
Genital organs	—	—	M TB, TB salpingitis	—	—	—	—	—
Pancreas	—	M TB	—	—	—	—	—	—
Thyroid	M TB	—	—	—	—	—	—	—
Gastrointestinal tract	—	—	—	—	—	—	—	—
Central nervous system	TB Gr in hippocampus and basal ganglia	—	—	—	—	—	—	—
Bone marrow	M TB	M TB	—	—	—	—	M TB	—
Miscellaneous	—	—	—	—	TB laryngitis with TB Gr	—	—	—
Cause of death	M TB, TB bronchopneumonia	M TB	M TB, TB bronchopneumonia	TB bronchopneumonia, disseminated TB	TB bronchopneumonia, disseminated TB	Disseminated extensive TB (pulmonary, myocardial)	M TB	TB bronchopneumonia

M TB, miliary tuberculosis; TB, tuberculous; TB Gr, epitheloid granuloma with central necrosis and infiltrate of lymphocytes, histiocytes, epithelial cells and Langhan's giant cells.

* Fibrin deposits in the small vessels of the viscera consistent with disseminated intravascular coagulation.

Examination of the aspirate from the knee effusion revealed thin, straw-colored fluid with few neutrophils and lymphocytes; no organisms grew in culture. A chest radiograph revealed bilateral diffuse infiltrates, consistent with a diagnosis of adult respiratory distress syndrome. A test for purified protein derivative of tuberculin was negative.

The patient became cyanotic and experienced severe respiratory distress; subsequently he became comatose. A picture of disseminated intravascular coagulation developed: platelets, 60,000/mL^3; fibrinogen, 60 g/dL, fibrin degradation product positive at 1:5 dilution, and prolonged prothrombin and partial thromboplastin times. The patient's course was marked by hypotensive episodes and oliguria, with BUN, 72 mg/dL and creatinine, 2.8 mg/dL. He expired on the 12th day after admission.

At autopsy, bilateral tuberculous bronchopneumonia with miliary tuberculosis involving the lungs, spleen, kidneys, adrenal glands, lymph nodes, thyroid, and bone marrow was noted. Fibrin thrombi were observed in the small vessels of the viscera.

Case 2. A 44-year-old man was admitted with fever, chills and cough with yellowish sputum of two weeks' duration, and abdominal pain, diarrhea and vomiting of one week's duration.

Physical examination revealed a respiratory rate of 28/min with moderate respiratory distress, bilateral coarse rales, and bronchial breathing in the lower lobe of the left lung. An examination of the abdomen revealed vague epigastric and right upper quadrant tenderness.

The chest radiograph was interpreted as showing evidence of bilateral diffuse pneumonia. A purified protein derivative test was negative. Antibiotic therapy with tobramycin and erythromycin was initiated. As the positive sputum acid-fast bacilli results became available, antituberculous therapy was instituted. The patient expired within 26 hours of admission. Significant autopsy findings included miliary tuberculosis of the lungs, pleura, liver, spleen, kidneys, bone marrow, and pancreas.

Case 3. A 32-year-old woman complained of vomiting, jaundice, fever, and cough for a week prior to admission. She also had irregular menses, the last period being eight months earlier.

Physical examination revealed a pulse of 190/min; temperature, 103°F; respiratory rate, 36/min; and scleral icterus. An examination of the chest revealed diminished breath sounds and vocal fremitus at the right base. In the abdomen, hepatomegaly was detected 16 cm below the right costal margin. Pelvic examination was normal.

The chest radiograph revealed atelectasis with pleural effusion of the right base and infiltrates of the lower lobe of the right lung. Cultures of the pleural fluid were negative for bacteria. Acid-fast bacilli were not detected in the smears. A purified protein derivative test was negative.

The patient received several antibiotics including gentamicin, chloromycetin, and cleomycin. Subsequently diarrhea and right upper quadrant pain developed. A diagnosis of cholecystitis was entertained. An exploratory laparotomy on the 35th hospital day revealed no abnormalities of the gall bladder; areas of saponification were noted in the mesentery and the omentum, with multiple adhesions between the loops of the small bowel. The pancreas was found to be indurated and an irregular, indurated mass was noted in the right upper quadrant. The patient had a stormy postoperative course and required a ventilator; she suffered several hypotensive episodes, became progressively anuric, and died on the 11th postoperative day.

Pertinent autopsy findings included tuberculous bronchopneumonia with miliary tuberculosis of the lungs, omentum, peritoneum, liver, kidneys, lymph nodes, and genital organs.

Case 4. A 34-year-old man sought treatment for a moderate fever, cough, and right pleuritic pain of a week's duration.

Examination revealed a right pleural effusion and a clinical picture of nephrotic syndrome, confirmed by laboratory data: urine albumin, 5 g/24 hr; serum albumin, 2.5 g/dL; serum cholesterol, 350 mg/dL. A purified protein derivative test was negative. The patient was treated with antibiotics, intercostal tube drainage of the empyema, and hemodialysis. He suffered several hypotensive episodes, became oliguric, and expired on the 24th hospital day.

At autopsy, the notable findings were tuberculous bronchopneumonia, tuberculous involvement of the pleura, peritoneum and spleen, and renal amyloidosis.

Case 5. A 74-year-old woman was admitted with hoarseness of the voice of three weeks' duration. Physical examination revealed no abnormalities. Laboratory data revealed a low Po_2, 58.9 mm Hg. Chest film was suggestive of active bilateral pulmonary tuberculosis. The sputum was positive for acid-fast bacilli. Other laboratory data were normal, except for an elevated lactate dehydrogenase, 260 U/L.

The patient was started on antitubercular therapy. At the start of the third hospital day the patient began to cough up thick, frothy sputum, and her respiratory status deteriorated. She expired on the eighth hospital day.

At autopsy, bilateral cavitary tuberculosis with tuberculous bronchopneumonia and tuberculous involvement of the liver, kidneys, and larynx were found.

Case 6. A 38-year-old woman with a history of chronic alcoholism was admitted in a state of marked agitation. Four years prior to admission she had been treated for pulmonary tuberculosis and had undergone excision of the upper lobe of the right lung.

Examination revealed a temperature of 99.4° F, severe respiratory distress with a respiratory rate of 32/min, and rales over both posterior lung fields. Sputum was positive for acid-fast bacilli. The chest radiograph showed diffuse alveolar interstitial infiltrates. Antitubercular therapy was initiated, but the patient expired on the third hospital day.

Autopsy showed extensive tuberculous involvement of both lungs and the myocardium.

Case 7. A 62-year-old woman with a history of diabetes mellitus—for which she took oral hypoglycemic agents, hypertension, and chronic renal failure, was admitted with fever and general body weakness of two days' duration.

No abnormalities were found on physical examination. Laboratory data revealed BUN, 143 mg/dL; creatinine, 7 mg/dL; uric acid, 10.2 mg/dL; blood sugar, 85 mg/dL; SGOT, 42 U/L; lactate dehydrogenase, 260 U/L; alkaline phosphatase, 102 U/L; hemoglobin, 4.1 g/dL; hematocrit, 14.5%. A peripheral smear revealed anisocytosis and poikilocytosis with target cells.

The patient underwent peritoneal dialysis. On the fourth hospital day she became febrile, with increasing respiratory distress. A right pleural effusion developed followed by a pericardial effusion. The patient expired on the 15th hospital day.

At autopsy, miliary tuberculosis of the lungs, pleura, pericardium, liver, spleen, kidneys, lymph nodes, and bone marrow was observed.

Case 8. A 75-year-old man with diabetes mellitus—for which he took oral hypoglycemic agents—was admitted in a state of severe respiratory distress. One week prior to admission he had a fever and complained of shortness of breath.

On examination, the patient was found to be stuporous, with pulse, 120/min; temperature, 103° F; respiratory rate, 30/min. Auscultation of the chest revealed bilateral scattered rhonchi. The chest film showed scattered interstitial infiltrates. Sputum cultures for bacteria and a smear for acid-fast bacilli were negative. Laboratory data and a computed tomographic scan of the head failed to show any abnormality.

A presumptive diagnosis of a cerebrovascular accident was made; the patient was put on ventilator support. He became comatose and expired on the 15th day after admission.

At autopsy, extensive bilateral tuberculous bronchopneumonia with candidal superinfection of the lungs was evident.

RESULTS

In all eight patients, significant and widespread tuberculous disease was evident at autopsy. In patients 2, 5, and 6 tuberculosis was diagnosed antemortem, but the disease took a fulminant course. Patients 1, 2, 3, and 7 showed miliary dissemination. All eight patients experienced severe respiratory distress, with cases 1 and 2 identified as having acute respiratory disease. Extensive tuberculous bronchopneumonia was noted in patients 1, 3, 4, 5, and 8. Patients 1 and 6 also had evidence of disseminated intravascular coagulation. Patient 3 had miliary involvement of the fallopian tubes, ovaries, and endometrium.

DISCUSSION

The cases described illustrate the fact that fulminant tuberculosis is still a concern, even with the availability of chemotherapeutic agents. Five of the eight patients (1, 3, 4, 7, and 8) were unusual in their clinical presentation, with tuberculous disease (TB) diagnosed for the first time at autopsy. Tuberculosis is recognized as a classic example of a disease with protean manifestations. In the United States it is estimated that more than 10 million people are infected with tubercle bacilli.[11] In 1982, 25,520 cases of TB were reported to the Centers for Disease Control, and in 19,050 of these *Mycobacterium tuberculosis* was isolated. This reflected a 6.8% decrease in the number of cases as compared to 1981.[11] While on the decline, the disease has by no means been eliminated. This is evident from many studies confirming active tuberculosis that is first diagnosed at autopsy.[1-3,7,8,12] Edlin[2] reported such findings in 12 out of 24 cases, and Andrion et al[7] quoted an incidence as high as 70%. In a study of 69 such cases, Enarson et al[12] emphasized that while the mortality rate due to tuberculous disease has decreased over the years, the number of deaths attributable to a failure of antemortem diagnosis of TB has slowly risen.

Miliary TB may develop as part of primary progressive TB or as a component of late generalized TB. In either situation, a massive lymphohematogenous spread occurs to various bodily organs. Of serious import is the concept of "cryptic TB," introduced by Proudfoot et al,[10] designating cases of disseminated TB that lack the typical clinical and radiologic features. In this series, patients 1, 3, 4, 7, and 8 qualify for this category. In patients 2, 5, and 6, although the diagnosis of TB was made, antituberculous therapy was begun too late to be effective, and the patients died within hours of diagnosis.

Various references in the literature allude to the changing epidemiologic pattern of the disease.[1-10] The common denominators stressed include advancing age, and the coexistence of risk factors such as diabetes mellitus, chronic renal failure, debility, malignancy, gastrectomy, and immunosuppression. Such risk factors were evident in this study in patients 2, 7, and 8 (diabetes mellitus), patients 2, 3, and 6 (alcohol dependency, which in turn, could predispose to malnutrition), and patient 7 (chronic renal failure). However, patients 1 and 4 were conspicuous for the lack of such associations, and their young age (26 and 34 years). These cases stress the importance of the need for a high index of suspicion as to tuberculous disease, even in apparently healthy individuals.

A review of the literature on active TB diagnosed postmortem reveals that the most common symptom is fever,[3,5] and the most frequent explanation for the fever is pneumonia. Fever is frequently accompanied by fatigue and abdominal pain, with serum alkaline phosphatase levels elevated in 81% of the cases.[5] Elevation of serum alkaline phosphatase levels is attributed to liver involvement in infiltrative disease, which is reported in 28% to 35% of cases.[9] In this study, six of eight patients experienced fever, and the significant elevation of alkaline phosphatase in patient 7 could be correlated with the tuberculous liver disease.

Miliary spread, meningitis, colonic TB, psoas abscess, and Addison's disease were diagnosed less often than pulmonary TB in Edlin's study.[2] Minor hematologic abnormalities including anemia and pancytopenia have also been reported.[5] Other unusual symptoms include disseminated intravascular coagulation[13] and thrombocytopenia,[14,15] both of which were seen in patients 1 and 6. The association with acute respiratory disease—as in patients 1 and 2—has also been described.[5] Amenorrhea is a common feature of genitourinary tuberculosis, as in patient 3, who had tuberculous endometritis, oophoritis, and salpingitis.

The classic diagnostic criteria for tuberculosis apply less often to the cryptogenic forms. A negative tuberculin test does not exclude the presence of active TB, as it may be a reflection of an immunosuppressed state; a negative test is often seen with fulminant TB, as in patients 1, 2, 3, and 4. To enhance the chances of detecting an organism, Bates[16] recommends examination of at least six to 10 sputum samples, while the American Thoracic Society[17] recommends a series of at least 3 consecutive samples on successive days. Aerosol induction could be used to stimulate the production of sputum. Hypertonic saline (2% to 10%) may be added to the aerosol generator or nebulizer. Gastric aspirates may also yield organisms, although only cultures are reliable, and the diagnosis, therefore, has to be delayed for six to eight weeks. As almost any anatomical site in the body may be involved, other specimens such as urine, cerebrospinal fluid, aspirates of effusions, pus, endometrial scrapings, and bone marrow or liver biopsies may be warranted.

In a study of 75 cases of acute miliary TB, Katz et al[18] found granulomas in 89% of bone marrow biopsies. The value of a liver biopsy is emphasized by Slavin.[6] Cerebrospinal fluid examination is recommended even in the absence of suggestive symptoms, due to the frequent involvement of the central nervous system.[19] The importance of chest radiographs cannot be over emphasized; however, in cryptic TB, the classic picture of miliary mottling may be absent.[10]

An appropriate evaluation and accurate diagnosis in atypical cases of disseminated TB have far-reaching implications. If the diagnosis is highly suggestive of tuberculous disease, it is recommended that even in the absence of demonstration of the organism, a therapeutic trial of antituberculous therapy should be promptly instituted. Undiagnosed TB can prove to be a potential hazard to the community, to the clinical staff, and to laboratory personnel.

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Prospects for disease eradication or elimination

ALAN R. HINMAN, MD

INTRODUCTION

The appropriate use of vaccines has enabled the eradication of smallpox from the globe and brought about remarkable reductions in the occurrence of other diseases in the United States (Table I). Greater than 99% reductions have been seen in virtually all of the diseases against which children are routinely vaccinated, demonstrating the kind of progress that can be achieved in a country such as the United States. Unfortunately, however, this type of impact has yet to be realized in the remainder of the world (Table II). In total, it is estimated that at least five million children die each year in the developing world as a result of diseases that can be prevented by vaccination.[1] More than 1.5 million children die each year in the world due to measles alone. By contrast, in the United States in 1983 there was only one measles death and that was in an infant who acquired measles while in the hospital.

This demonstration of what can be achieved through the use of vaccines and other preventive measures has led to a consideration of the feasibility of eradicating certain diseases.

DEFINITIONS

To understand some of the factors involved, it is necessary to establish some definitions. The *Oxford English Dictionary* defines eradication as "the action of pulling out by the roots, total destruction, extirpation." [2]

Cockburn defined eradication as the "extinction of the pathogen that causes the infectious disease in question; so long as a single member of the species arrives, then eradication has not been accomplished. The definition implies action on a worldwide scale." [3] Using this definition, it is possible that Cockburn would not consider smallpox to be eradicated, since smallpox virus is maintained in two laboratories in the world, albeit under tight security.

Soper said that the objective of eradication was the complete elimination of "the possibility of occurrence of a given disease, even in the absence of all preventive measures." [4] Finally, Andrews and Langmuir defined eradication as the "purposeful reduction of specific disease prevalence . . . to the point of continued absence of transmission within a specified area." [5]

There are some differences in these definitions, but they all share the concepts that eradication is a purposeful act and that the term should not be applied to the disappearance of a particular pathogen or disease in the absence of specific eradication efforts. Although not necessarily stated overtly, they also share the concept that after an initial period of effort, measures against the disease can be terminated without reappearance of the disease. This carries with it a global implication, which was made explicit in Cockburn's definition. Although Cockburn agrees that "regional" eradication could be achieved, he states that this "implies a basically unstable situation because at any time the infection may be reintroduced by carriers or vectors from outside." [3] Soper states that "eradication can, therefore, be regarded as that state in which the infection does not return from infected areas after control measures have been abandoned. If procedures have to be continued to prevent return of the infection, then the state is one of control and not of eradication." [4]

Without wishing to enter any new definitions, I suggest that it is useful to consider a spectrum of disease incidence, with five levels that depend on the degree of success of the efforts taken against the disease (Fig 1). In the natural state, disease incidence is affected by the traditional triad of host, agent, and environment, and although evolutionary changes might lead to disappearance of the disease, there is no specific control action.

The application of specific measures to reduce the occurrence of a disease may lead to a situation of control, in which continuing efforts leave the occurrence of the disease at a reduced, but presumably acceptable, level. This is the situation with many infectious diseases in the United States at present. From a state of control, elimination of a disease from a particular area can be achieved. In this situation, the disease no longer occurs on a continuing basis in the area, but the threat of reintroduction of disease from outside this area (with subsequent reestablishment of transmission) is so great that continuing control efforts are required. This situation describes our short-term goal for measles and rubella in the United States.[6,7] As the risk of reintroduction of disease is lowered through measures applied in other countries, regional eradication may be attained. In this case it would not be necessary to pursue actively the control

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Presented at the United States Public Health Service Professional Association 19th Annual Meeting, Scottsdale, Arizona, June 4, 1984.

Address correspondence to Dr Hinman, Director, Division of Immunization, Center for Prevention Services, Centers for Disease Control, Atlanta, GA 30333.

TABLE I. Comparison of Maximum and Current Morbidity of Vaccine-Preventable Diseases

Disease	Maximum Cases (Yr)		1983	Percent change
Diphtheria	206,939	(1921)	5	−100.00
Measles	894,134	(1941)	1,436	−99.84
Mumps*	152,209	(1968)	3,285	−97.84
Pertussis	265,269	(1934)	2,258	−99.15
Polio (paralytic)	21,269	(1952)	8	−99.96
Rubella†	57,686	(1969)	953	−98.35
Congenital rubella syndrome	20,000+	(1964–5)	20	−99.20
Tetanus††	601	(1948)	75	−87.52

* First reportable in 1968.
† First reportable in 1966.
†† First reportable in 1947.

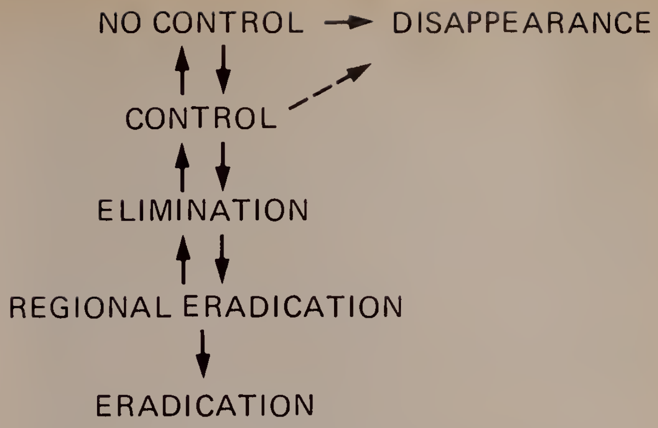

FIGURE 1. Spectrum of disease incidence.

TABLE II. Burden of Vaccine-Preventable Diseases*

Percent of all babies born in the developing world
- 1.0% will die of neonatal tetanus
- 2.0% will die of pertussis
- 3.0% will die of measles
- 0.5% will become lame from polio

* Source: WHO Expanded Programme on Immunization

measures; surveillance and prompt response to importation are capable of maintaining the area free of disease. This represents the present status of malaria in many countries and islands. The final leap, from regional eradication to global (or "true") eradication, would only occur when all areas had achieved regional eradication. To date, smallpox is the only example of a disease which has been truly eradicated.

HISTORY OF ERADICATION EFFORTS

Interest in disease eradication has existed for many years; both Thomas Jefferson and Edward Jenner believed vaccination would ultimately rid the world of smallpox. Even though these sentiments were published, organized attempts to stamp out infectious disease did not begin until late in the 19th century. These efforts were primarily aimed at animal diseases including pleuropneumonia of cattle in the United States and animal rabies in England. The successful regional eradication of yellow fever from Cuba in the early years of the 20th century gave rise to hopes that world eradication of the disease could be achieved. The subsequent discovery of a separate cycle of yellow fever transmission outside of urban areas which would pose a continuing threat even if *Aedes aegypti* was eradicated led to diminished enthusiasm for global yellow fever eradication. However, the concept of disease eradication through vector control or elimination found a practical expression in the successful eradication of a highly effective mosquito malaria (*Anopheles gambiae*) from Brazil. This mosquito species was introduced from Africa to Brazil in 1930 and within a few years caused major epidemics of malaria in the northeast section of the country. Fortunately, the species had not established itself throughout the country, and it preferred to breed in shallow sunlit pools which could be easily identified. In Soper's words,

> *A gambiae* was eradicated from Brazil by inspectors, each carrying an empty pail and a small container of Paris green, who routinely visited and dusted all potential *A gambiae* breeding areas within a carefully delineated geographic area for which each was responsible.[8]

The program was successful after a two-year period of operation during which strict supervision was essential. As an example of the type of supervision involved, Soper wrote,

> Once organized, meticulous administration seems logical and simple and it belied the difficulties suffered in its development. Unavoidably, such administration was criticized at times by someone who overlooked the serious responsibility of the Yellow Fever Service. The press in Niteroi once violently attacked the Service for dismissing an inspector because he had not been killed the day before. The inspector's itinerary required him to spend much of the same morning each week in the arsenal across Guanabara Bay from Rio de Janeiro. On the morning of one scheduled visit, the arsenal was destroyed by an explosion and every one on the premises perished. The press insisted that the Yellow Fever Service should have rejoiced over the inspector's escape rather than penalize him for dereliction in performance of his duty.[8]

This categorical programmatic approach, with extraordinary demands of perfection in the carrying out of duties, became an integral part of future eradication efforts with malaria and with smallpox.

The demonstration that dichlorodiphenyltrichloroethane (DDT) sprayed inside the walls of houses could kill infected anopheline malaria vectors led to regional eradication of malaria from many areas, particularly islands, and to the development of the concept of worldwide malaria eradication. In 1955, the World Health Assembly voted to sponsor a program for world malaria eradication. The objective was defined in the following way:

> Malaria eradication means the ending of the transmission of malaria and the elimination of the reservoir of infective cases in a campaign limited in time and carried to such a degree of perfection that, when it comes to an end, there is no resumption of transmission.[9]

Major effort was placed on this activity and the United

States government supported the program both through financial contributions to the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF), and through the bilateral provision of foreign aid for malaria eradication through the Agency for International Development, with technical assistance from Centers for Disease Control (CDC). Unfortunately, global eradication did not prove as easy as regional eradication had been. Major problems arose in both the administrative and the technical areas. In some countries, an administrative structure that could establish the stringent supervision required did not exist. Technically, the development of vector resistance to DDT shattered the hopes of rapid eradication in some areas. To make matters worse, the initial success in eliminating malaria opened up many areas to rapid agricultural development, which led to major influxes of new residents to those areas and called for a degree of flexibility in planning which often was not present. In consequence, the goal of global eradication of malaria has not as yet been achieved. However, regional eradication has been achieved in sizeable portions of the world.

Four other diseases have been proposed for global eradication: smallpox, guinea worm disease (dracunculiasis), yaws, measles.[10] Smallpox has been eradicated as a result of an extraordinary, intensive, international effort.[11] Efforts to eradicate guinea worm disease are under development,[12] and an international conference has recently discussed the potential of yaws eradication.[13] Although the desirability of measles eradication is generally accepted, there is no consensus on whether it is yet technically or administratively feasible.[14-18]

DISEASE ERADICATION CONSIDERATIONS

Proponents of global disease eradication share an attitude toward the occurrence of disease that is different from that of most public health workers. As Soper has stated,

> In control, one may measure progress from the high point on the curve of incidence downward, ie, what has been done; in eradication one measures always from the base line of the chart upward, ie, what remains to be done. In control, one tends to lose interest in a disease at the point where, in eradication, many times, the greatest difficulties are encountred.[8]

Similarly, Cockburn has said that, "The last 5% is as important as the first 95%. Anything less than 100% is not eradication." [3] Cockburn has also listed five program needs for eradication to be achieved: political stability, popular support, adequate organization, efficient quarantine system, and sustained effort; the last being the most important.

Clearly, consideration of a disease for eradication is not a task to be undertaken lightly. In fact, Henderson, who coordinated the successful WHO Smallpox Eradication Program, has said,

> I now see no other candidate disease for global eradication—no other disease with the appropriate combination of severity and suitable epidemiologic characteristics and for which we have appropriate and affordable technology to permit eradication.[11]

In proposing a disease as a candidate for eradication, Hinman listed eight criteria that should be considered: (1) Is eradication technically feasible? (2) Is eradication economically feasible? (3) What is the impact of the disease? (4) Is the eradication proposal economically feasible globally? (5) Is there international appeal for the undertaking? (6) Are there personnel available? (7) Will a vertical program slow down emergence of well-rounded public health programs? and, (8) What are the economic consequences of failure to eradicate?[19]

These questions are as valid in 1984 as they were in 1966. They must be kept in mind in developing plans for eradication of guinea worm disease and yaws and in considering whether to advance the battle of measles from elimination to global eradication. Global measles eradication is both necessary and inevitable. However, it is not likely to be achieved in the short run. It will certainly not be achieved if we do not successfully demonstrate national elimination and, probably, regional eradication. In this regard, it is important to note that there are six other countries that have declared goals of measles elimination (Canada, Czechoslovakia, Finland, Norway, Sweden, and the Soviet Union) and that a working group has called for the regional elimination of measles from Europe.[20] Achievement of this goal will be important in setting the stage for ultimate eradication of measles.

Not everyone believes that measles eradication is technically feasible, and most feel that the present stage of development of immunization services around the world is not adequate to achieve the goal. Nonetheless, it seems a highly desirable objective, given the burden that measles poses. From our own national point of view, eradication is an important target since, even when measles is eliminated from this country, it will be necessary to maintain immunization levels and vigilant safety measures until measles is successfully brought to a state of control (or possibly, eradication) in the rest of the world. Although measles elimination is clearly cost effective, continuation of efforts to control measles in the United States will cost between $25 and $50 million per year for immunization, surveillance, and outbreak control.[21] From a purely economic point of view, it may be important to support a global eradication effort.

MEASLES ELIMINATION

Even though eradication does not seem to be a feasible goal for most diseases, elimination certainly is. In 1978, the goal was set to eliminate indigenous measles by October 1, 1982. The elimination strategy had three main components: achievement and maintenance of high immunization levels, strong surveillance, and aggressive outbreak control. An important ingredient in achieving and maintaining the immunization levels has been the enactment and enforcement of school immunization requirements; all 50 states require measles immunization prior to first entry to school, and in 42 states these laws affect all grade levels from kindergarten to the 12th grade. One result of these laws has been the fact that 97% of the children entering school for the first time have been immunized against measles. The reported incidence of measles has declined dramatically since vaccine licensure (Fig 2) and reached a record low level in 1983, when only 1,436 cases were reported. Ninety-six percent of the nation's counties reported no measles at all during the year, and all counties were free of measles for at least six consecutive weeks at some time during the year, indicating that transmission had ceased.[22]

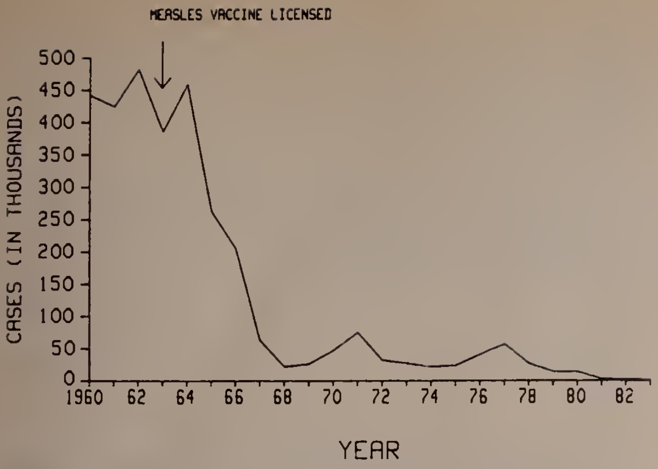

FIGURE 2. Reported cases of measles in the United States, 1960–1983.

In 1984, unfortunately, there has been some upswing in the reported incidence of measles, with 1,327 cases reported in the first 21 weeks of the year, compared with only 817 in the same period of 1983. This 62% increase reflects, primarily, three outbreaks occurring in California, Michigan, and Texas.[23] Although this increase is of some concern, careful investigation of the outbreaks has indicated that, in general, they are a result of inadequate vaccination levels, and that the basic strategy is sound, albeit somewhat overdue. Successful elimination of measles in the near future is anticipated.

OTHER CANDIDATES FOR ELIMINATION

Several other vaccine-preventable diseases have virtually been eliminated from the United States, including poliomyelitis, diphtheria, and tetanus. In 1982 and 1983 only 21 cases of polio were reported in the United States. All were caused by oral polio vaccine virus. This indicates the degree of control achieved over wild polio virus disease. It also indicates the continuing need to balance the benefits and risks of vaccination and to continually reevaluate the respective advantages of inactivated and oral polio vaccines. Only one case of diphtheria occurred in a child in the United States in 1983; it occurred in an unvaccinated 14-month-old. More than 60% of all cases of tetanus in the United States occur in persons over the age of 60. Very few cases have ever occurred in people who have been fully immunized.

Both rubella and mumps are clearly susceptible to elimination. The intensification of efforts to hasten the elimination of rubella is just beginning. By contrast, the public health burden posed by mumps is not great, and it does not seem appropriate to undertake intensified efforts to hasten its disappearance.

In addition to these infectious diseases, there are many other conditions that are candidates for elimination, such as Rh hemolytic disease of the newborn, tobacco-induced disease, injury and death resulting from not using seat belts, lead paint induced disease, and other man-made diseases or exposure to toxic substances. With prevention and control measures these conditions can be eliminated, but control efforts must be maintained to ensure that they do not reappear. Many of these conditions represent only segments of the total problem; for example, traffic fatalities do occur even when the passengers wear seat belts. The fact that some traffic fatalities are not a result of failure to use seat belts, however, should not be allowed to impede attempts to eliminate all traffic fatalities which are due to such carelessness. It is necessary to define carefully what is intended to be accomplished, and to ensure that no one has false expectations. In addition, it is important to understand that there is a sizeable latent or incubation period for many of these conditions, and thus effects may not be seen immediately. Thus, even if all tobacco use in the United States stopped today, it would be several years before tobacco-related lung cancer disappeared.

An issue that is sometimes raised with regard to non-infectious, behavioral conditions is that they represent outcomes of individual choice and do not pose dangers to others, as do communicable diseases. Consequently, it may be alleged that it is inappropriate to try to affect these behaviors. The fact is that these conditions pose a terrible drain on family members, health insurance plans, and taxes to support care for patients with illnesses such as cigarette-induced lung cancer or chronic obstructive pulmonary disease, or those whose paraplegia could have been prevented by use of seat belts. We not only have the right, we have the duty to try to reduce this suffering (and expense).

It must be foreseen that as the conditions we seek to eliminate become infrequent, other causes for the condition will become more prominent. For example, if all cigarette smoking stopped, over the years lung cancer not associated with cigarette smoking would become the only type of lung cancer seen. This might lead to statements that eliminating tobacco use would no longer be necessary since tobacco was not causing lung cancer. Additionally, as the condition itself becomes less frequent, the risks associated with the control measure become relatively more prominent. This has been evident particularly with the polio vaccine. For example, if all individuals wore seat belts, all traffic fatalities would occur in individuals who were belted. This might lead to demands for abandonment of the use of seat belts, particularly since there may be a few instances in which seat belt use actually contributes to fatality by trapping an individual inside the vehicle.

It is necessary to develop the attitude that certain conditions are preventable and to investigate and categorize each occurrence of the condition as preventable or not preventable. For example, in the measles elimination field, any case of measles that occurs in an individual of proper age to have received vaccine, but who has not received it, is considered preventable. If a case occurs in someone who is too young or too old to be vaccinated, or if it occurs in an individual who has been vaccinated, it is considered a non-preventable case. Along with the development of the concept of preventability goes an acknowledgment of responsibility for the prevention of these occurrences. This acknowledgment and the subsequent commitment to prevention must include not only the public health community but also the private medical community and the public at large. Developing this attitude may be one of the most important tasks and one of the most difficult.

The investigation and classification of conditions as preventable or not preventable also gives valuable clues as to strategies that may be necessary to bring about their elimination. These strategies may involve individual or collective action. For example, in the immunization arena, one of the most effective means of improving immunization levels has been the enactment and enforcement of school immunization requirements. Several states have already enacted seat belt legislation for children, but this addresses only part of the problem. Enactment and enforcement of seat belt legislation for adults has been shown to have a substantial impact on the occurrence of traffic fatalities[24] in other countries and would be a valuable addition to prevention efforts in this country.

In the 1980 prevention objectives from the Public Health Service, important goals have been set for reduction of several diseases.[25] Although these goals are important and will represent major accomplishments if achieved, we should look beyond achievement of these objectives toward the elimination of that which can be feasibly eliminated. As preventionists, it seems inappropriate to aim for less.

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STATE CARE OF TUBERCULOUS PATIENTS

A few suggestions as to some of the means we can employ in arousing the public to the point of action, before considering the best and most economical methods of providing treatment and care for the consumptive, are submitted.

In the first place I would suggest that the crusade against consumption be made a popular one, even a fashionable one, if you will. In this respect follow the example of our European confrères. Let associations be formed similar to the admirable Pennsylvania Association for the Prevention of Tuberculosis, and have sections or local societies in various portions of the State; hold frequent public meetings with *laymen* of note and influence as sponsors and speakers; enlist the daily press, and have such meetings widely reported; let frequent articles appear in the papers upon the importance and urgency of the problem. In England, as you know, the daily press was a potent factor in arousing the interest and enthusiasm of the people. Local societies sprang up all over that country, and money was contributed for prevention and the erection of sanatoria for the open-air treatment; and the work is now in full progress. Once the public is thoroughly aroused it will quickly respond, the fearful will act from motives of self-protection, and the philanthropist from humane considerations.

I will now consider the best methods to advocate for the suppression of this disease and the treatment and care of those afflicted with it. In the solution of this problem we have the example and experience of Europe to aid us, to which I shall refer later. Besides the educative efforts in the way of tracts and circulars by societies and boards of health regarding the danger from sputum and its avoidance; disinfection and renovation of abodes occupied by consumptives or in which a death from this disease has occurred; ordinances regarding the spitting nuisance in public conveyances and places of gathering; cuspidors conveniently placed in halls, shops, and wherever people may congregate; laws and ordinances regarding cattle, meat, and milk inspection; the free examination of sputum; besides all this most important field of effort, there remains the greater and absolutely essential complement to it—namely, provision for the treatment, care, and isolation of the poor consumptive, a task far too enormous for private or even municipal effort, but in which the aid of the State must be invoked.

EDWARD O. OTIS, MD
Transactions of MSSNY 1900, pp 78–79

A 56-year-old man with fever, a changing heart murmur, anemia, and hepatosplenomegaly

CASE PRESENTATION

Rosemary Kalendarian, MD (Resident, Medical Service): A 56-year-old man was admitted with fever, fatigue, and increasing intensity of a heart murmur.

While working at his usual occupation as a carpenter, 10 days prior to admission, the patient noted unusual fatigue with effort. The following day, he had loss of appetite, chills, and fever with temperatures to 101°F, unrelieved by aspirin. Subsequent persistent fever for one week (99° to 103°F) was initially attributed at a local emergency room to poor dentition and gingivitis; at that time his hematocrit value was 29% and erythrocyte sedimentation rate 129 mm/hr. Further persistence of symptoms after a course of penicillin therapy led to the observation at the same emergency department that a systolic murmur described on the previous visit as grade I/VI had increased in intensity to grade II/VI, and admission to the Veterans Administration Medical Center was advised.

The patient had been unaware of a heart murmur and had taken no medications prior to the onset of symptoms. He had smoked one pack of cigarettes a day for many years until one year prior to admission.

On admission the patient was thin and pale, but in no acute distress. Blood pressure was 140/70 mm Hg; pulse rate, 96/min and regular; respirations, 20/min; and temperature, 102°F. Examination revealed multiple, firm, nontender, mobile cervical and inguinal lymph nodes up to 1 cm in greatest dimension; a 2-cm node was present in the left axilla. Poor dentition was present. Examination of the heart revealed normal first and second heart sounds; a grade III/VI systolic murmur was present at the left lower sternal border with radiation to both carotid arteries. The liver was palpable two finger breadths below the right costal margin, and the spleen was palpable three finger breadths below the left costal margin. There was no evidence of blood in the stool on Hemacult® test. The skin showed splinter hemorrhages on the upper extremities, but was otherwise normal. The neurologic examination was within normal limits.

Urinalysis indicated a specific gravity of 1.010, with negative tests for glucose, protein, and bile; the microscopic examination showed occasional white blood cells. The hemoglobin was 9.5 g/dL; hematocrit value, 22.5%; mean red blood cell volume, 78 μ^3 (normal range, 80 to 94 μ^3); white blood cell count, 9,400/mm^3 with 58% polymorphonuclear leukocytes, 3% band forms, 17% monocytes, and 21% lymphocytes (80% of which were atypical). The platelet count was 94,000/mm^3; the erythrocyte sedimentation rate was 139 mm/hr. The serum sodium was 125 mEq/L; serum potassium, 4.8 mEq/L; serum chloride, 93 mEq/L; serum bicarbonate, 26 mEq/L; blood urea nitrogen, 23 mg/dL; serum creatinine, 1.4 mg/dL; and serum glucose, 156 mg/dL. The serum albumin level was decreased (2.6 g/dL); serum alkaline phosphatase was 200 units/L (normal, 30 to 115 U/L); serum lactate dehydrogenase, 483 U/L (normal, 60 to 200 U/L); serum glutamic pyruvic transaminase (SGPT), 135 U/L (normal, 0 to 45 U/L); serum glutamic oxalic transaminase (SGOT), 94 U/L (normal, 0 to 41 U/L); serum triglyceride level, 443 mg/dL (normal, 30 to 135 mg/dL). The prothrombin time and partial thromboplastin time were normal. A chest roentgenogram showed no abnormality of the heart, lungs, or mediastinum. The electrocardiogram was within normal limits.

Six blood cultures obtained 48 hours or more after the discontinuance of penicillin therapy were reported as negative for bacterial growth. The Monospot® test for infectious mononucleosis, serum test for hepatitis B antigen, cytomegalovirus antibody titer, rheumatoid factor test, and panel of skin tests for anergy (purified protein derivative, mumps, and Candida) were all negative. Toxoplasma immunoglobulin antibody titers were positive in dilutions to 1:256. Serum febrile agglutination tests were negative except for positive titers for paratyphoid A and B in dilutions of 1:160.

A 2-D echocardiogram revealed annular calcification of the aortic valve but no evidence of vegetations, mitral stenosis, or aortic insufficiency. The cardiology consultant believed that the patient's murmur was compatible with aortic valve sclerosis. The liver-spleen scan confirmed the hepatosplenomegaly.

By the eighth hospital day, the patient was afebrile and remained so for the remainder of his hospital stay. Additional laboratory studies indicated a reticulocyte count of 0.8%; normal serum levels of vitamin B_{12} and folate; a normal level of haptoglobin; a negative Coombs' test; serum iron, 4 μg/dL (normal range, 42 to 135 μg/dL); total serum iron-binding capacity 468 μg/dL (normal range, 280 to 400 μg/dL). The bone marrow was hypercellular with adequate megakaryocytes and diminished iron stores. A computed

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Based on the clinicopathologic conference (CPC) held at the Veterans Administration Medical Center, Northport, NY, on April 11, 1984.

Moderator: Edward Gogel, MD, Assistant Professor of Clinical Medicine, SUNY at Stony Brook; *Clinical Discussion:* David M. Horowitz, MD, Instructor in Medicine, SUNY at Stony Brook; *Pathology Presentation:* Carl Ilardi, MD, Assistant Professor of Pathology, SUNY at Stony Brook.

Editor: JOHN T. FLYNN, MD.

Address correspondence to Dr Flynn, Consulting Editor, *New York State Journal of Medicine*, PO Box 5404, 420 Lakeville Rd, Lake Success, NY 11042.

tomographic (CT) scan of the abdomen revealed a normal liver size but marked splenomegaly; the para-aortic lymph nodes were not enlarged but appeared to contain areas of calcification. Serum protein electrophoresis showed increased gamma globulins; the serum protein immunoelectrophoresis indicated an elevated serum IgG level of 3,205 mg/dL (normal range, 800 to 1,800 mg/dL); the IgA and IgM levels were normal.

A diagnostic procedure was performed.

CLINICAL DISCUSSION

David M. Horowitz, MD (Instructor in Medicine, SUNY at Stony Brook): The history describes a patient who either suffered with an acute illness or experienced the sudden decompensation of a more indolent one. The only suggestion of a gradual decline in health was the progressive loss of weight.

In line with the tendency of many patients to relate incorrectly the onset of a gradually progressive disease to discrete events, there was considerable evidence here to suggest a prolonged indolent course of the patient's illness. At the time of admission there was generalized adenopathy, palpable splenomegaly, mild hepatomegaly, and fever. A cardiac murmur had increased in intensity over a few days' time. Linear subungual hemorrhages were present. The erythrocyte sedimentation rate was markedly increased; there was severe anemia with a slightly low mean corpuscular volume, a decrease in serum iron level, and an increased iron-binding capacity. Thrombocytopenia and an absolute monocytosis were present. Despite the normal number and percentage of lymphocytes, many atypical forms were seen. The peripheral smear that I examined showed no evidence of hemolysis or of extramedullary hematopoesis. The serum albumin level was low, and the globulins were increased. The serum sodium was low, the BUN and creatinine mildly increased, as were the alkaline phosphatase, SGOT, SGPT, and lactate dehydrogenase. The urinalysis showed no protein or active sediment.

The temperature curve indicated a febrile course for several days after admission, but thereafter the temperature returned to normal without antibiotic or other specific therapy. The blood cultures were negative. The patient remained severely anemic; the reticulocyte response was minimal; and the serum iron was low, whereas the total iron-binding capacity was increased. The bone marrow was described as hypercellular with diminished iron stores but was otherwise normal. The SGOT level decreased toward normal, and the serum albumin level improved but remained at subnormal levels. The serum IgG was increased, but the electrophoretic pattern did not show a monoclonal spike. The toxoplasma IgG antibody titer was 1:256. The Monospot® test, hepatitis B surface antigen, and core antibody tests were negative. Serum tests for rheumatoid factor and rapid plasma reagin agglutination test for syphilis were negative, as were the skin tests for purified protein derivative, mumps, and Candida.

At this point I will ask Dr Michael Clair to review the x-ray films for us.

RADIOLOGY PRESENTATION

Michael Clair, MD (Chief of Radiology Service): The admission posteroanterior chest film was within normal limits; however, on the lateral view there was a subtle suggestion of hilar fullness. Oblique roentgenograms or 55-degree oblique hilar tomography might have been helpful; but on these films, the finding is at best equivocal.

Films of the abdomen taken on admission indicate marked enlargement of both the liver and spleen, extending down to the pelvic brim.

CT scan of the abdomen taken on admission, with oral contrast, suggests a somewhat smaller liver than does the plain film, but the spleen is tremendously increased in volume. Intravenous contrast studies might have been helpful in identifying any focal defects in either the liver or the spleen.

Enlargement of retroperitoneal nodes would be indicated by an increase in the absolute size of individual nodes beyond 15 to 20 mm, often the result of invasion by neoplasm. Careful study of this patient's CT scan created an impression of an increase in the number of visualized small or normal-sized nodes, which raised the possibility of neoplastic involvement. This suspicion could be confirmed with the aid of lymphangiography.

On the CT scan, densities are visible within several lymph nodes at the level of the aortic bifurcation. They probably represent calcification within the nodes, rather than the retention of contrast medium from a previous lymphangiogram.

Dr Horowitz: This patient's systemic illness was manifested by primary or secondary involvement of the lymphoreticular system with generalized adenopathy and pronounced splenomegaly. Second, the anemia best fits the category of decreased red blood cell survival or sequestration with inadequate marrow response, without evidence of marrow replacement or extramedullary hematopoiesis. Third, the cardiac murmur increased in intensity, which may suggest primary involvement of the endocardium by an infectious, ischemic, or infiltrative process. However, the murmur might have been intensified by such nonspecific factors as anemia, fever, and dehydration causing a hyperdynamic state. And fourth, there was a marked polyclonal increase in IgG, which could be due to a variety of infections and inflammatory states associated with increased B-cell stimulation.

A number of clinical entities is suggested by these major diagnostic points, including certain infections, collagen vascular diseases, malignancies, chronic lymphadenopathies with systemic manifestations, and other entities such as sarcoidosis, drug-induced or vaccination-induced conditions, and graft-versus-host reactions.

At the time of admission, infective endocarditis must have seemed a likely diagnosis because of the fever, heart murmur, adenopathy, splenomegaly, anemia, and elevated sedimentation rate. The splinter hemorrhages would be more suggestive of infective endocarditis if found in the proximal rather than the distal portions of the nail beds, but these details are not given. The patient's occupation, that of carpentry, affords numerous opportunities for trauma to the fingers. In any event, neither the echocardiogram, the characteristics of the murmur, nor the six negative blood cultures rule out the diagnosis of infective endocarditis. Although the percentage is diminishing, about 10% of the cases of infective endocarditis are still reported as culture-negative in such situations as right-sided endocarditis caused by relatively noninvasive organisms, or infections due to organisms with fastidious growth requirements or to nonbacterial organisms such as fungi, chlamydia, or rickettsia.

Two pivotal points mitigate against the diagnosis of infective endocarditis. First, the patient suffered from a severe systemic illness with fever and he defervesced without antibiotic therapy. Subsequently no other sequelae of infective endocarditis developed in the hospital setting where they would have been readily observed. Second, although splenomegaly occurs in a third of patients, it is rare to find splenic enlargement of this magnitude that can be attributed solely to infective endocarditis.

Infectious mononucleosis is well known to cause fever, adenopathy, splenomegaly, and polyclonal hypergammaglobulinemia. This condition could also account for the abnormal liver function tests and the atypical lymphocytes seen on the peripheral smear. It is more common in young people but occurs in older adults as well. However, the infrequency with which this infection causes such profound systemic illness weighs against this diagnosis. Also, the serologic and hematologic information do not support this diagnosis. The Monospot® test was negative; and, although 80% of the lymphocytes counted on the peripheral smear were atypical, the absolute number and percentage of lymphocytes were normal.

Visceral leishmaniasis or kala-azar can present with this constellation of findings and is well known to cause massive splenomegaly. However, the vector for transmission is one of a number of sand flies that are not endemic to the United States. Since there is no history of recent travel to India, Africa, the Middle East, or to South or Central America, we can dismiss this possibility.

Toxoplasmosis is another protozoal illness that can be associated with the symptoms described. Its distribution is worldwide. Contrary to what one may expect, the toxoplasma IgG titer of 1:256 constitutes negative rather than positive evidence of recent infection, whereas an elevated toxoplasma IgM titer would be suggestive of recent infection. Adenopathy occurs late in the course of the infection, at a time when IgG titers are expected to be high, that is, greater than 1:1000. A toxoplasma IgG titer of 1:256 in the presence of lymphadenopathy makes the diagnosis unlikely.

Cytomegalovirus (CMV) sometimes presents in this manner in severely immunocompromised hosts. However the patient was not known to be immunosuppressed, and the serum CMV titer is negative.

Secondary syphilis is often accompanied by lymphadenopathy. Splenomegaly can also occur in a florid case. Such findings, especially splenomegaly, are uncommon at later stages. A nonreactive rapid plasma reagin test in secondary syphilis would be most unusual.

Cat scratch fever is characterized by local rather than generalized adenopathy. Severe constitutional symptoms are rare.

The physical findings and chest roentgenogram are not suggestive of either primary or reactivated pulmonary tuberculosis; however, this does not exclude the diagnosis of miliary tuberculosis. Although 90% of patients with miliary tuberculosis will eventually have the classic roentgenographic findings, patients may initially present with a normal chest film. Of particular interest to our discussion, splenomegaly or adenopathy occurs in 15% of the cases even though massive splenomegaly is rare. Liver function tests, especially the serum alkaline phosphatase levels, are frequently abnormal. Hyponatremia due to inappropriate secretion of antidiuretic hormone has been well documented. The purified protein derivative skin test is initially negative in 25% of the patients with miliary tuberculosis.[1] At the time of hospital admission, this diagnosis should have been a serious consideration because it is a treatable illness with a dismal prognosis if left untreated.[1]

Turning our attention to collagen vascular diseases, splenomegaly, lymphadenopathy, and hypergammaglobulinemia are all common in rheumatoid arthritis and Felty's syndrome. However, the total absence of joint manifestations in the presence of severe systemic illness precludes these diagnoses. We might postulate adult Still's disease, a form of rheumatoid arthritis in which systemic inflammatory disease is present without prominent articular manifestations. However, 86% of the patients with adult Still's disease experience its onset before the age of 36, and in nearly all patients arthralgias and skin rash develop. Systemic lupus erythematosus causes fever, lymphadenopathy, and splenomegaly; but it would be difficult to invoke this diagnosis in the absence of any manifestations of joint, skin, renal, cardiac, or neurologic disease.

Peripheral lymphadenopathy, splenomegaly, fever, and hypergammaglobulinemia have all been observed in sarcoidosis. No laboratory test unequivocally establishes the diagnosis. A diagnosis of sarcoidosis implies that widespread characteristic granulomas are present in several organs and no other cause for these granulomas can be found. In fewer than 10% of the cases of sarcoidosis the patients initially have extrathoracic manifestations and normal chest films, and an even smaller percentage have lymphadenopathy and splenomegaly.

Reversible lymphadenopathy with systemic manifestations, including fever and splenomegaly, has been well documented in patients taking phenytoin and other anticonvulsant drugs. However, this patient was not known to have taken any such medication. The short course of penicillin was initiated after the onset of his illness.[2]

Vaccinations and graft-versus-host reactions can also cause a similar symptom-complex, but the history gives no suggestion of such occurrences.

In the category of malignancies, adult leukemias, especially the acute forms, and idiopathic myelofibrosis can present with lymphadenopathy, fever, and splenomegaly. It is noteworthy that the physician who examined the patient in the emergency room diagnosed gingivitis, since myelomonocytic and monocytic leukemias are frequently accompanied by gum infiltrates. In chronic lymphocytic leukemia, enlargement of the spleen, liver, and lymph nodes is common; fever without infection is not common but can occur. Richter's syndrome, which is thought to be a kind of lymphomatous transformation that occurs in association with chronic lymphocytic leukemia, presents clinical similarities to the illness of the patient under discussion. However, given the presumed advanced stage of this patient's illness, none of these possible diagnoses is compatible with the patient's peripheral blood smear or the bone marrow aspirate findings.

Kaposi's sarcoma can present with this constellation of findings, sometimes in association with hypergammaglobulinemia. This lesion was previously seen predominantly in elderly men and African children, but it has received much attention recently because of its association with acquired immune deficiency syndrome (AIDS). Kaposi's sarcoma is usually accompanied by characteristic skin nodules, but no such nodules were mentioned in the protocol. However, it has been known to occur without such nodules in some African children and in patients with AIDS.

Multiple myeloma rarely presents with this clinical picture. However, a subgroup of patients with an IgG neoplasm and a Waldenström-like syndrome has been identified. These patients and patients with true Waldenström's disease can present in the manner described. However, such patients would all be expected to display a monoclonal component on serum protein electrophoresis. Light-chain disease, when present, generally is characterized by osteolytic lesions. Of the remaining plasma cell dyscrasias, the only one that is compatible with the clinical findings is gamma heavy-chain disease, since it is frequently accompanied by lymphadenopathy and hepatosplenomegaly and sometimes by fever without infection. Furthermore, although patients with gamma heavy-chain disease always have monoclonal protein components, these can be missed on routine serum protein electrophoresis.

Hodgkin's disease is a major possibility. Although this disease commonly appears with painless enlargement of lymph nodes in younger patients, it frequently occurs in older patients with fever, lymphadenopathy, and splenomegaly. Fever persists for several days and then tends to remit spontaneously. Although this patient experienced only one febrile interval, this fever course is compatible with the Pel-Ebstein pattern associated with Hodgkin's disease. The peripheral blood smear and the defects in delayed hypersensitivity are also compatible with Hodgkin's disease.

Among the non-Hodgkin's lymphomas, the follicular lymphomas typically present without major systemic symptoms. Diffuse large-cell lymphomas are associated with a more localized but rapidly expanding tumor mass, often at extranodal sites. Symptoms are frequently attributable to invasion or compression. Burkitt's lymphoma is primarily an extralymphatic tumor. Lymphoblastic lymphomas are seen in younger patients and usually present with mediastinal adenopathy.

The entities classified as chronic lymphadenopathy with systemic manifestations have several characteristics in common: their causes are unknown, and they are associated with proliferation within the lymphoreticular system, each with characteristic histologic features of a benign hyperplastic process. Giant lymph node hyperplasia has two distinct pathologic forms. The less common type, known as the plasma cell form, usually presents as a large solitary nodal mass, most often in the mediastinum, and often in association with anemia, hepatosplenomegaly, and hypergammaglobulinemia. However, a few cases of multicentric lymphadenopathy have been described. The median age of patients at the time of diagnosis is the mid-twenties, although a recent report indicated its occurrence in three elderly men with multicentric giant lymph node hyperplasia. Two of the three also had Kaposi's sarcoma.[3,4]

Sinus histiocytosis with massive lymphadenopathy are associated with greater lymph node enlargement. Hypergammaglobulinemia is common, and systemic symptoms can occur. However, in 80% of the patients, the onset of their illness occurs before 20 years of age.

Immunoblastic lymphadenopathy is a recently described entity with clinical and histologic findings similar to Hodgkin's disease. It involves mixed cellular proliferation in lymph nodes without Reed-Sternberg cells.[5] Angioblastic lymphadenopathy with dysproteinemia is a similar entity, and there is disagreement among various investigators as to whether the two conditions might be identical. The National Library of Medicine groups them together under the single heading "immunoblastic lymphadenopathy." Its cause and pathogenesis are unknown but are presumed to involve a non-neoplastic hyperimmune proliferation of the B-cell system, with transformation of lymphocytes into immunoblasts and plasma cells. Most patients are over 50 years of age and usually present with generalized lymphadenopathy, hepatosplenomegaly, fever, weight loss, and sometimes a pruritic skin rash. Laboratory tests reveal polyclonal hypergammaglobulinemia and anemia sometimes due to Coombs'-positive hemolysis. Delayed sensitivity skin tests for mumps, Candida, and purified protein derivative are usually negative. The erythrocyte sedimentation rate is markedly elevated and, interestingly, strongly positive serologic tests for toxoplasmosis are sometimes observed.[2,5,6] Despite the benign characteristics of the lymph node histology, the result is often a progressive, fatal illness.

Lukes and Tindle,[6] who were among the first to describe this entity, postulated that immunoblastic lymphadenopathy is a prelymphomatous disorder. They cited examples of progression to an entity with definite malignant histologic characteristics known as immunoblastic sarcoma. According to Lukes, the development of immunoblastic sarcoma in a patient with immunoblastic lymphadenopathy is often heralded by the enlargement of nodes and a dramatic change in the intensity of systemic symptoms.[6] Patients have been identified in whom immunoblastic lymphadenopathy and immunoblastic sarcoma were present in different portions of the same node, all at the time of their initial clinical presentation. This suggests that immunoblastic lymphadenopathy may have existed for some time without recognition of its clinical state. With the possible exception of a flare of systemic symptoms at the time of transformation, the two entities, immunoblastic lymphadenopathy and lymphoblastic sarcoma, seem indistinguishable.[6]

In reviewing the most probable entities in the initial differential diagnosis, we have eliminated all but a few. Those that still bear consideration are miliary tuberculosis, gamma heavy-chain disease, sarcoidosis, Hodgkin's disease, immunoblastic lymphadenopathy, and immunoblastic sarcoma. The diagnostic procedure that was carried out was probably a lymph node biopsy.

Miliary tuberculosis was an important entity to consider initially. However, no microbiologic evidence of infection or subsequent abnormalities on the roentgenogram were described. Furthermore, the patient defervesced without antituberculous therapy. Although gamma heavy-chain disease is quite rare, we should still consider it at this point mainly because in the serum protein electrophoresis a monoclonal spike of heavy chains can be missed. It is unlikely that any single diagnostic procedure would support this diagnosis, unless that procedure were immunoelectrophoresis using monospecific antiserum against gamma heavy chains.

Sarcoidosis remains in the running because of its protean nature; admittedly, the clinical presentation here would be unusual for sarcoidosis. In the absence of other characteristic clinical, roentgenographic or laboratory evidence of the disease, a single diagnostic procedure would not permit the diagnosis of sarcoidosis. Similarly, for a diagnosis of Kaposi's sarcoma we would have to postulate its occurrence without characteristic skin lesions, which would be uncommon. In addition, the patient did not fit into either of the two groups in which Kaposi's sarcoma has been reported without skin nodules, that is, among children in Africa and among patients with AIDS.

The pivotal piece of information that supports a diagnosis of immunoblastic lymphadenopathy over Hodgkin's disease is hypergammaglobulinemia. The IgG level is only sometimes elevated in Hodgkin's disease, but it is almost invariably elevated in immunoblastic lymphadenopathy. The study by Wagner et al[7] described measurements of quantitative immunoglobulin levels in 51 patients with Hodgkin's disease and 102 normal controls. Although 20% of the patients with Hodgkin's lymphoma had increased IgG levels, the increase was usually small. Of the patients with Hodgkin's lymphoma, all but two had a serum IgG of less than 2 g/dL, and none was above 2.7 g/dL.[7] The patient described in the protocol had a quantitative IgG of 3.2 g/dL.

My final diagnosis is immunoblastic lymphadenopathy. I will ask you to recall my previous comments about the course of the patient's illness. He may have had an indolent illness preceding his presentation in the emergency room. Thus, I would not dismiss the possibility that the patient's symptoms flared, marking a transition from immunoblastic lymphadenopathy to immunoblastic sarcoma.

CLINICAL DIAGNOSIS

Immunoblastic lymphadenopathy with possible transition to immunoblastic sarcoma.

PATHOLOGY PRESENTATION

Carl Ilardi, MD (Assistant Professor of Pathology, SUNY at Stony Brook): The diagnosis offered by Dr Horowitz is entirely reasonable. It would have been very difficult to determine the correct diagnosis in this case solely on clinical grounds, since it depends upon examination of the histopathology of the lymph node that is biopsied. This patient has an immunoproliferative disorder that resembles Castleman's disease—that is, giant lymph node hyperplasia—in its multifocal form. The basic architecture of the lymph node in this case is preserved. Characteristically, there is marked vascular proliferation within the germinal centers that are surrounded by prominent concentric rings of mature lymphocytes (Fig 1). A reticulum stain shows this marked angiomatous proliferation involving not only the germinal centers but also the interfollicular zones (Fig 2). Close scrutiny will reveal the presence of immunoblasts in this disease. Dr Horowitz mentioned that there are two histopathologic variants of this condition—the hyaline-vascular type, not usually associated with any systemic involvement, and the plasma-cell type. In the latter, there is a proliferation of plasma cells that can be very prominent. I believe this patient has a form of the disease intermediate between the two major varieties; some microscopic areas demonstrate characteristics of the hyaline-vascular variety, whereas in other fields there are sheets of plasma cells (Fig 3), as are seen in the plasma-cell variant of giant lymph node hyperplasia. There also were atypical lymphocytes in the peripheral blood (Fig 4). These are a reflection of the activated state of the patient's immune system. Careful review of the bone marrow aspirate reveals evidence of localized plasma cell hyperplasia. This has been reported in the multifocal variant of Castleman's disease.[8]

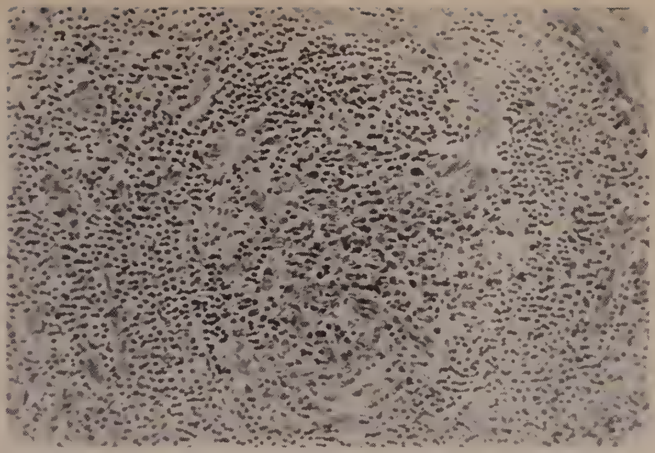
FIGURE 1. Lymph node biopsy specimen showing germinal center surrounded by concentric layers of mature lymphocytes. (hematoxylin and eosin stain; original magnification × 20)

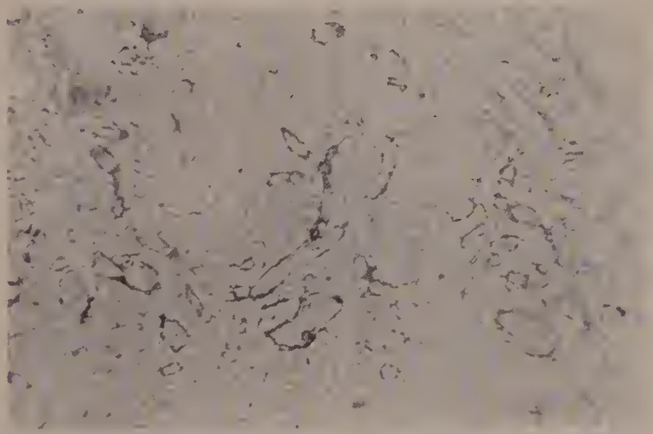
FIGURE 2. Proliferation of blood vessels, outlined by reticulum stain, between follicles of lymph node. (hematoxylin and eosin stain; original magnification × 10)

In 1956 Castleman et al[9] described this condition as a lymph node hyperplasia localized to the mediastinum, with local symptoms related only to the presence of a space-

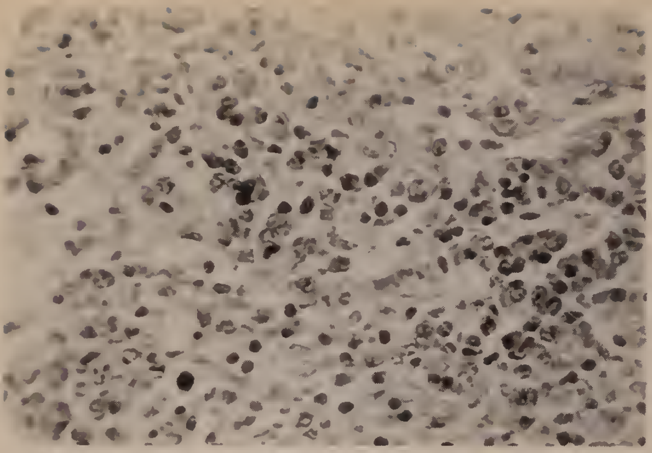

FIGURE 3. Plasma cell proliferation within lymph node in areas between follicles. (hematoxylin and eosin stain; original magnification × 40)

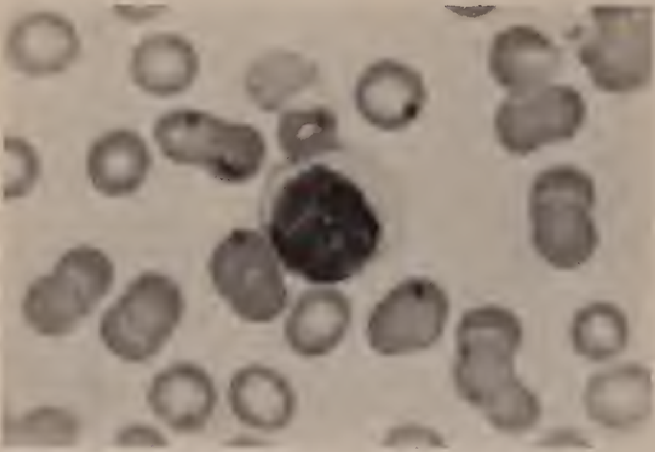

FIGURE 4. Atypical lymphocyte in peripheral blood. (Wright-Giemsa stain; original magnification × 100)

occupying lesion in that area. Subsequently, Keller and associates[10] reported cases in which the systemic findings included fever and anemia.

A recent report from the University of Minnesota and the Mayo Clinic of 15 patients with multicentric giant lymph node hyperplasia syndrome indicated an age range from 41 to 74 years, with a median age of 57 years.[8] These patients had systemic findings that included fever, night sweats, and weight loss; generalized lymphadenopathy was found in all the patients, and hepatosplenomegaly was common. Two patients had Kaposi's sarcoma. Unspecified renal abnormalities and skin rashes were also noted. The patients in this study had a mild to moderate anemia; in some of these patients, there was evidence of an antierythropoietin factor that might account for the development of the anemia. Polyclonal hypergammaglobulinemia was found in most of these patients, usually with increases in IgG, IgM, and IgA.[8] The patient in this report underwent a radioimmunodiffusion study that indicated an increased IgG at the time of his initial presentation. He continues to have increased IgG, divided between kappa and lambda light chains, so that the increase is not strictly monoclonal but is at least bitypic. There were no abnormal arcs on immunoelectrophoresis.

What happens to these patients? Originally, it was reported that they followed a benign course[9,10] after resection of the lymphoid mass. It is now clear, however, that at least in the multicentric variant a good outcome does not necessarily follow.[8,11] Frizzera et al[8] divided the patients into three groups: in four patients the course was aggressive and led to death within five to 14 months; in four other patients survival was from 30 to 42 months. The remaining patients continued to have a smoldering course with symptom-free periods punctuated by recrudescence of the disease. The indolent course in these patients lasted from 39 to 222 months. Sixty percent of the patients with giant lymph node hyperplasia in Frizzera's study died. A recent summary of the experience of the Rappaport group included 16 patients with the multicentric variant; of these, 62.5% died.[11]

The death of patients with giant lymph node hyperplasia is often due to sepsis,[8] although progression to lymphoma[8,11] and disseminated immunoproliferative disease with multiorgan involvement[8] has also been reported.

The pathogenesis of this disease is unknown, although several possibilities have been suggested. The disease may be a normal response to some unknown antigen or antigens. This might be the case in classic Castleman's disease, in which there is a localized hamartomatous proliferation of lymphoid tissue in the thorax, perhaps as a result of exposure to some antigen via the airways. The condition can involve the mesentery, and speculation suggests that perhaps some antigen has gained access to the gastrointestinal tract, resulting in this proliferation. It is more difficult to explain the multicentric variant, and some investigators have suggested that this is an abnormal immune response.[8,11,12] The evidence for this possibility is based on a number of observations summarized by Frizzera et al.[8] Spleens have been studied and have been found to have areas of T-cell depletion; the Rappaport group has similarly demonstrated T cell depletion in some of their cases.[11] The disease is associated with advanced age, a time at which the immune system is depressed. There has been more than one instance of associated Kaposi's sarcoma, which is known to be associated with immune deficiency. There have been related autoimmune phenomena including arthritic disorders and the production of an anti-erythropoietin factor.

The presence of immunoblasts and plasma cells indicates a marked B-cell proliferation, but it is not yet known whether this is the primary disorder or the result of abnormal T-cell modulation of B-cell maturation.

Is giant lymph node hyperplasia related to immunoblastic lymphadenopathy? No cases have demonstrated an evolution or transition of this type of histology into immunoblastic lymphadenopathy. If morphology is critical in the differentiation of disease processes, then these two conditions are different diseases, since the histopathologic changes are different.

Edward Gogel, MD (Assistant Professor of Clinical Medicine, SUNY at Stony Brook): This patient has continued to do well up to the present time without treatment and has returned to work.

Thomas Rush, MD (Instructor in Medicine, SUNY at Stony Brook): One question that has not been answered is the reason for the iron-deficiency anemia. He had a low serum iron level, low iron stores in the bone marrow, and an elevated total iron-binding capacity.

Hosein Zarrabi, MD (Hematologist-Oncologist): I have reviewed this patient's bone marrow, and it shows the presence of adequate iron stores with no evidence of ring sideroblasts. Therefore, the patient does not have an iron-deficiency anemia. There were increased numbers of mature plasma cells in the marrow aspirate and clot section.

Dr Rush: That must be the most likely explanation. Despite the bone marrow findings, the serum iron and total iron-binding capacity were suggestive of an iron deficiency anemia. However, the lesson to be learned is that when the laboratory tests do not conform to the clinical picture, we have to discard the laboratory tests.

My other question relates to the impression in the protocol that this patient's adenopathy was not prominent. He had a single large lymph node in the left axilla. Is this usual with these patients, and where do you see the lymph node involvement? How widespread is it? He did not have any retroperitoneal involvement.

Dr Gogel: The patient had some enlarged cervical nodes as well as the submaxillary node, but they were not very large.

Dr Ilardi: The name "giant lymph node hyperplasia" is derived from Castleman's original description of the large hamartomatous lymphoid masses that he observed. The patients do not have to have massively enlarged nodes.

Benjamin Luft, MD (Assistant Professor of Medicine, SUNY at Stony Brook): Would the pathologist comment on the character of the proliferation of these B cells, as to whether it is monoclonal, polyclonal, or a mixture of monoclonal and polyclonal cells? Secondly, can he also compare the pathology seen in this disorder with that seen in immunosuppressed transplant recipients who have what is presumed to be an Epstein-Barr virus (EBV)-induced B cell lymphoproliferative disease? Has anyone made any EBV serologic studies in the group of patients with giant lymph node hyperplasia that might suggest they have an ongoing EBV infection?

Dr Ilardi: I cannot answer the second part of the question; EBV induces diffuse polymorphous proliferation of lymphocytes with numerous immunoblasts, quite unlike that seen here. I do not know of any studies that relate EBV infection to giant lymph node hyperplasia.

As far as the monclonality of the condition, the patient's latest serum protein immunoelectrophoresis shows that there is an increase in IgG, but it is equally divided between kappa and lambda light chains. Could that go along with lymphoid malignancy? Yes, it can; there are instances of lymphoma that are bitypic—that is, the IgG is divided between kappa and lambda.

This patient does not have the elevations of IgM and IgA that have been reported in the literature; I do not know why. We tried to stain this lymph node by immunoperixodase to demonstrate monoclonality, but the plasma cells would not stain, perhaps because of a problem with fixation.

Dr Luft: An article in the *New England Journal of Medicine* reported Cleary's experience that, in the B-cell lymphoproliferative disease associated with transplantation, the cells very often would not stain on the surface for immune globulins.[13] A DNA analysis was used to prove B-cell monoclonality, even when immunoglobulin was not present on the cell surface or even within the cell.

Dr Ilardi: I know that gene rearrangement is now the way to identify T and B cells, but it is quite a special procedure that we cannot do, either at the university or here.

Hidenori Kawanishi, MD (Gut Mucosal Immunity Laboratory): Have either the surface markers or the functional capabilities in vitro of these atypical lymphocytes been studied?

Dr Ilardi: No, we have not performed such tests in this case.

Dr Kawanishi: Could you tell me the difference between giant lymph node hyperplasia and angioimmunoblastic lymphadenopathy?

Dr Ilardi: The major difference involves the morphology of the lymph node. In immunoblastic lymphadenopathy there is a tendency for the normal architecture of the lymph node to be obliterated; in giant hyperplasia, there is a preservation of the architecture, with maintenance of prominent germinal centers. These centers are usually absent in immunoblastic lymphadenopathy or are almost totally obliterated, leaving only a small amount of connective tissue at the site of previous centers. In angioimmunoblastic lymphadenopathy, the proliferation of immunoblasts is much more than that seen here; also in giant lymph node hyperplasia, there usually is or can be a tremendous proliferation of plasma cells, which is not seen in immunoblastic lymphadenopathy. In immunoblastic lymphadenopathy, the cellular proliferation can extend beyond the capsule of the lymph node; this does not occur in giant lymph node hyperplasia.

The morphology suggests that these are different diseases and, consequently, they may well be.

Barry Coller, MD (Professor of Medicine and Pathology, SUNY at Stony Brook): If it is any comfort, I would have made the same diagnosis as Dr Horowitz. A young patient I knew with angioimmunoblastic lymphadenopathy followed a clinical course very similar to that of this patient, with a fatal outcome. We are recognizing that a larger number of so-called benign lymphohistioproliferative disorders can have a lethal outcome. We should not be lulled into a sense of confidence simply because the lymph node architecture has not been effaced. In fact, some of these diseases are as lethal as diseases in which lymph node effacement, diagnostic of malignancy, is found. This patient illustrates a disease process about which we will no doubt hear more in the future, as new molecular probes of surface proteins and DNA become available.

Dr Ilardi: In the series of case studies that I presented, the pathologists were not able to find any features that would predict how these patients were going to behave as regards outcome, that is, which cases would terminate in death. The patients in whom lymphomas developed did not present any areas of cytologic atypia or clustering of abnormal proliferations within the lymph nodes.

FINAL DIAGNOSES

Giant lymph node hyperplasia (Castleman's disease).

Anemia suggestive of iron deficiency, of unknown cause, possibly related to production of an antierythropoietin factor.

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See also pp 515–517.

FROM THE LIBRARY

HOW THE MEDICAL PROFESSION CAN HELP LEGISLATORS RESOLVE ISSUES OF MUTUAL CONCERN FROM THE SENATE'S POINT OF VIEW

I believe that those who run the Medical Society do a good job of informing doctors at the grass roots of what is going on, but from that point I think your program sags badly. During the session, any session, I receive letters from say a Dr "X" who is head of "Y" medical society telling me how the medical profession feels in his county on a particular issue; but the other members in that society show a complete lack of understanding whenever I speak to them. In other words your communications are breaking down between the head of the society and the doctors who are out on the firing line.

Now, let's talk about public relations a little further. The first time I ran for office, I received a letter from our local medical society two days before the election asking for my stand on socialized medicine. At that time this was a very volatile subject which produced much heat and little enlightenment. I answered in the best way I knew how but as soon as the election was over I heard nothing about it. I haven't to this day. It was merely an effort to make a candidate dance so the whole profession would know where he stood and I say that is not a good way to improve public relations with persons who hold public office...

There are a lot of other issues that you should be interested in but they, generally speaking, go by the board. I am going to give you one illustration. In 1957 we had a bill which would have required Blue Cross plans to include podiatrists. Now I am not going to discuss with you today the merits of podiatry. I don't think it is relative to the situation. The chief point is that the greatest problem for the Blue Cross and Blue Shield Plans is their flexibility. If you require them to absorb new benefits willy-nilly, these may kick them right out of business because commercial carriers with their deductibles and their coinsurance features are in a much better competitive position than either the Blue Cross or the Blue Shield. We all know that. Therefore, I think that no matter how good podiatry is, it is a dangerous precedent to require that these various insurance plans carry something that they may not want to carry. If you can do this one year through the Legislature, what is to prevent the chiropractors from coming next year, getting enough support, and saying that the Blue Cross must care for them too? Now you see how this proposition was dangerous and why I had letters from your various local groups saying they were very averse to this legislation.

But what happened? I couldn't get a corporal's guard to support me on the floor of the Legislature on this particular subject. I spoke against it and I think there were all told about four or five who felt the same way that I did, but the majority of senators voted to include podiatric aid. Their lobby worked continuously to build up friendly relations and they were successful. Now, whether the podiatrists are officially in or out, and I think the matter is in the courts, it is a dangerous thing and we should be very careful not to put Blue Cross and Blue Shield Plans in an economic strait jacket.

I say to you today that if you feel about this the way I feel, then it behooves you, wherever you are, to contact your legislators and talk to them. Don't just call them on the phone, but go and see them and tell them how you feel and explain the dangers that lurk beneath the surface. Blue Cross and Blue Shield are basically your programs. The service benefit idea didn't come from commercial carriers. You proposed it yourselves.

SENATOR GEORGE R. METCALF
(*NY State J Med* 1959; 59:1135–1136)

Giant lymph node hyperplasia associated with heavy proteinuria

MICHAEL J. CROOK, MD, KATHLEEN M. SHAHEEN, MD, WOONG MAN LEE, MD

Since the original description by Castleman,[1] giant lymph node hyperplasia (GLH) has been documented as a distinct, albeit rare, pathologic entity. Numerous clinical abnormalities have been associated with this tumor, incuding myasthenia gravis,[2] refractory anemia,[3-5] and nephrotic syndrome.[6,7] Although many theories exist, the cause of the glandular hyperplasia is still unknown.

We describe a case of GLH with several unique features: nephrotic-range proteinuria, a positive direct antiglobulin (Coombs') test, and giant-cell reaction in histologic tissue sections in the setting of past breast augmentation surgery. Unusual to this case is the presence of these clinical findings with the hyaline-vascular type of GLH.

CASE REPORT

A 27-year-old woman experienced progressive dyspnea and orthopnea for four days' duration. She had been in excellent health and denied having recent weight loss, fever, or edema. There was no history of previous transfusions or intake of medications. She denied any previous kidney disease but stated that elevated protein levels had been detected on a routine urinalysis two months previously. Six years before the onset of symptoms, she had undergone bilateral breast augmentation surgery with silicone gel implants. An admission chest roentgenogram revealed a large mediastinal mass with massive pleural effusion on her left side.

Physical examination revealed a well-nourished woman who became dyspneic with minimal exertion. Her vital signs were normal. Breath sounds were diminished on the left, and there was dullness to percussion to the level of the scapula. No lymphadenopathy, hepatosplenomegaly, or abdominal masses were detected. The remainder of the examination was normal.

Initial laboratory values were within normal limits except for those reviewed in Table I. Noteworthy results included a mildly decreased serum albumin level, positive Coombs' test, abnormal urinalysis results, and heavy proteinuria. Straw-colored fluid was obtained from preoperative thoracentesis. Routine culture and cytologic examination results were negative. A chest roentgenogram after thoracentesis revealed a soft-tissue mass in the medial part of the left apex with central stellate calcification. A massive pleural effusion and partial collapse of the left lung were also noted (Fig 1). A computerized tomographic (CT) scan of the chest confirmed the roentgenographic findings of a large mass arising from the left side of the pleura (Fig 2). No hilar or mediastinal lymphadenopathy was noted. An abdominal CT scan was negative. At surgery, a 5 × 4.5 × 3.5-cm pleura-based mass was excised; her postoperative course was uneventful.

Six weeks after surgery, the patient's condition was reevaluated. Her physical examination was normal, and no recurrence of the mass or effusion could be seen on roentgenograms. Repeated laboratory evaluations revealed normalization of the serum albumin level and urinalysis results. A direct Coombs' test remained weakly positive. There was dramatic resolution of proteinuria to less than 1 mg in 24 hours (Table I). One year after the initial diagnosis and treatment, the patient remains asymptomatic.

Pathologic findings. The gross specimen was encased in a thin fibrous capsule and weighed 58 g. The cut surface appeared tan and fleshy, with radiating central calcification.

On microscopic examination, the lymph node was composed of diffuse follicular centers and vessels ensheathed by wide cuffs of hyalinized fibrous connective tissue. The interfollicular regions contained small lymphocytes, immunoblasts, and a few plasma cells. Foreign body-type multinucleate cells were present on some sections without polarizable material or associated granulomas (Fig 3).

The histologic findings were consistent with the hyaline-vascular rather than the plasma-cell pattern of GLH, with the unique feature of foreign body-type giant cell reaction.

DISCUSSION

Giant lymph node hyperplasia is a rare, benign, and localized enlargement

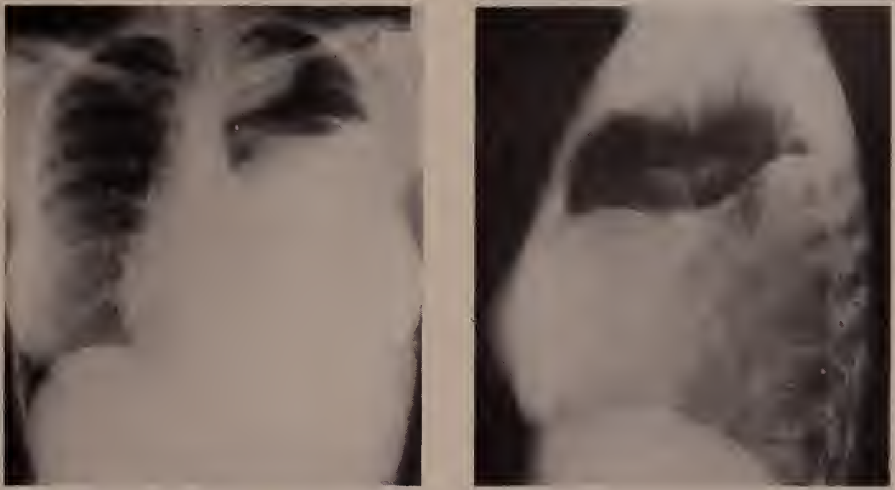

FIGURE 1. Chest roentgenograms showing left apical mass, pleural effusion, and pneumothorax after thoracentesis.

From the Departments of Medicine (Dr Crook) and Pathology (Drs Shaheen and Lee), Glens Falls Hospital, Glens Falls, NY.

Address correspondence to Dr Crook, 62 Elm St, Glens Falls, NY 12801.

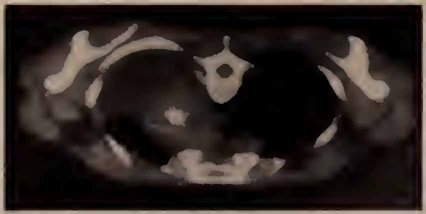

FIGURE 2. Computerized tomographic scan of chest revealing pleura-based mass (arrows) with central calcification and massive pleural fluid (F).

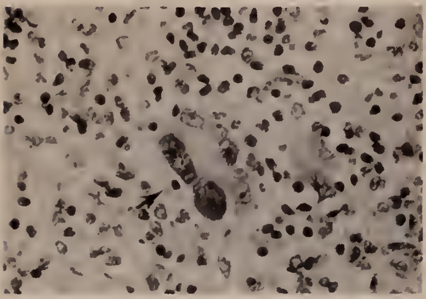

FIGURE 3. High-power view of area with multinucleate giant cell (arrow) (hematoxylin and eosin, original magnification X 400).

of lymph nodes. This entity has various synonyms, including angiofollicular lymph node hyperplasia, angiomatous lymphoid hamartoma, benign giant lymphoma, follicular lymphoreticulosis, and others.[8] The variety of names applied to the lesion reflect speculation regarding its etiology and pathogenesis. Two types of lesions have been described histologically with varying clinical manifestations.[9] The hyaline-vascular type, which is most common (80% of cases), is usually devoid of symptoms and found on routine chest x-ray examination. The less-common plasma cell type is associated with hematologic abnormalities including refractory anemia, hypoferremia, elevated sedimentation rate, hypoalbuminemia, and hyperglobulinemia. Systemic findings include fever, sweating, fatigue, lymphadenopathy, splenomegaly, growth failure, and others.[8] Generally, with excision of the mass, the abnormalities tend to normalize within 30 to 60 days.

Nephrotic syndrome associated with GLH has been reported in two case studies. The first case involved a mesentery-based mass, and renal biopsies revealed a minimal-change glomerular lesion.[6] In the second case only the thymus was involved, but myelofibrosis was also present.[7] The tumor in both of these cases, however, favored the plasma-cell variety. The case described here was of the hyaline-vascular type, with the unique feature of focal giant-cell collections. Although nephrotic syndrome did not exist in our patient, nephrotic-range proteinuria did. Dyspnea from her massive pleural effusion probably prompted a diagnosis before edema and severe hypoproteinemia could develop. The prompt return to normal of her renal functions after excision of the tumor supports the existence of a relation between the two.

How this tumor provokes nephrosis is unknown, but numerous hypotheses exist. An attractive theory is that circulating immune complexes cause glomerular injury, and proteinuria develops as a consequence. In other tumors, including those of Hodgkin's disease, the presence of tumor-associated antigen and host gamma globulin have been demonstrated on the glomerular basement membrane.[6,10] The tumor producing a toxic substance that alters basement-membrane permeability is another possibility.[6] Amyloid deposition and lymphomatous infiltration have also been postulated as causes but seem unlikely in the patient described here.[10] Unfortunately, no renal biopsy was performed on this patient.

The presence of a positive, direct antiglobulin test is an interesting and previously unreported finding in this entity. It certainly lends credence to the belief that circulating antibodies are present that may have been induced by the pleura-based tumor. The tumor, therefore, may have provoked an autoimmune response and been directly responsible for the associated clinical abnormalities.

Multinucleate giant cells have never been described in this lesion, and their importance is conjectural at best. It is possible that their origin stems from the prostheses from previous breast augmentation. Leeching of the silicone gel contained in breast implants has been reported, and capsules surrounding the implants have revealed "droplets" of material that proved to be silicone.[11] This patient's specimen and surrounding lymph nodes were examined for silicone, polarizable material, and granulomas, but none were detected.

Numerous possible causes have been proposed for GLH. The presence of eosinophils, plasma cells, reticular lymphoblasts, and capillary proliferation in the hyaline-vascular lesions suggests an inflammatory or infectious process. The extensive follicular hyperplasia and sheets of plasma cells of the plasma cell lesions are a hallmark of an immune response to antigenic stimuli. Some authors suggest that the two lesions represent variants of the same process, deriving their distinct qualities from differences in host response.[8] Whether the source of antigen is viral particles from infection, host antigen creating an autoimmune response, or some unknown nonspecific antigen is purely speculative. It was interesting that breast augmentation surgery in this patient preceded the onset of the illness by six years. Whether a cause-and-effect relationship exists will remain a pertinent but unexplained question.

Acknowledgment. Irene M. Billow provided secretarial assistance in preparing this article.

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TABLE I. Pertinent Laboratory Data From Initial Hospitalization and Postoperative Evaluation

Test Taken	Measure at Admission	Measure at Reevaluation
Serum		
Creatinine level	0.9 mg/dL	0.8 mg/dL
Albumin level	3.5 g/dL	4.4 g/dL
Direct Coombs	Positive	Positive
	Anti-IgG, 2+	Anti-IgG, weakly positive
	Anti-C3d, negative	Anti-C3d, negative
	Anti-Fy, positive	Anti-Fy, positive
Urine		
Urinalysis	Specific gravity, 1.032 pH, 5.0, albumin, 4+ 2-4 WBCs/high-power field 1-5 RBCs/high-power field 2-4 granular casts	Normal
Creatinine clearance, 24 hr	79 mL/min	105 mL/min
Total protein level, 24 hr	3.5 g	<1 mg

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See also pp 507–514.

An unusual cause of subclavian steal syndrome

CHARLES A. JUNGREIS, MD, JAMES B. NAIDICH, MD, MICHAEL G. PERSICO, MD,
CARMINE MOCCHIO, MD, HARRY L. STEIN, MD

Transient episodes of cerebral ischemia can be attributed to many causes. One particularly intriguing entity has been the subclavian steal syndrome.[1,2] We recently treated a patient whose symptoms closely resembled those of the subclavian steal syndrome. However, further evaluation disclosed the presence of a vertebral artery-vertebral vein fistula that was responsible for the symptoms.

CASE REPORT

A 63-year-old man sought treatment for progressive weakness of the left upper extremity accompanied by dizziness and transient visual disturbances. On physical examination, a bruit was audible over the left side of the neck.

Angiographic examination of the aortic arch revealed an intact left subclavian artery and no antegrade filling of the left vertebral artery. Delayed films revealed retrograde filling of the more distal left vertebral artery (Fig 1). A subsequent right vertebral artery injection demonstrated flow from the right vertebral artery to the left vertebral artery with reversal of flow through the left vertebral artery. The reversed flow through the left vertebral artery continued through a fistula with the vertebral vein, with eventual opacification of the subclavian vein (Fig 2).

In this case a catheter technique for closure of the fistula was not recommended because the proximal vertebral artery was already occluded. There was no direct angiographic access to the arterial feeder. A surgical approach seemed simpler.

At surgery, the occlusion of the origin of the left vertebral artery was confirmed. The vertebral artery was traced upward until the communication between the patent distal vertebral artery and the numerous dilated veins was identified. These vessels were ligated. This resulted in relief from the symptoms and elimination of the bruit.

DISCUSSION

The classic subclavian steal syndrome[1,2] is the result of an occlusion of the subclavian artery proximal to the origin of the vertebral artery. Instead of both vertebral arteries contributing blood to the brain as a result of their anastomosing to form the basilar artery, this anastomosis serves as a major collateral to supply the normal distribution of the occluded subclavian artery. There is flow up one vertebral artery and reversed flow down the other. Blood is "stolen" from the basilar circulation to supply the arm.

The case reported here is another cause for relative ischemia to the basilar circulation because of reversal of flow through one of the vertebral arteries. Blood flow through the fistula into the venous circulation occurred preferentially to the normal flow through the vertebral arteries into the brain.

To date, approximately 80 cases of vertebral artery-venous fistulas have been reported.[3] The most common cause has been penetrating trauma. War injuries were usually implicated in the past. Currently, iatrogenic causes, especially needle puncture wounds, are responsible.[4] In this patient, a central venous line placed during previous abdominal surgery was the likely cause. Rare cases have been seen in association with the arterial lesions of fibromuscular dysplasia[3] and neurofibromatosis.[5]

The usual presentation of such vertebral artery-venous fistulas is as a noise or buzzing in the neck that is audible to the patient.[4] This case was unusual in that there was no such complaint. Rather, the

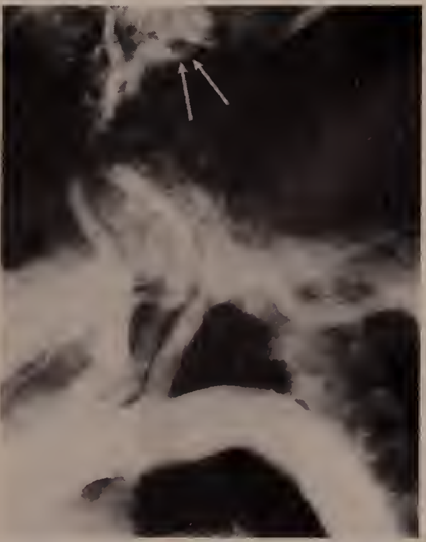

FIGURE 1. Aortic arch injection. Retrograde opacification of distal left vertebral artery (arrows).

From the Departments of Radiology (Drs Jungreis, Naidich and Stein) and Surgery (Drs Persico and Mocchio), North Shore University Hospital, Cornell University Medical College, Manhasset, New York.

Address correspondence to Dr Naidich, Professor, Department of Radiology, North Shore University Hospital, 300 Community Drive, Manhasset, NY 11030.

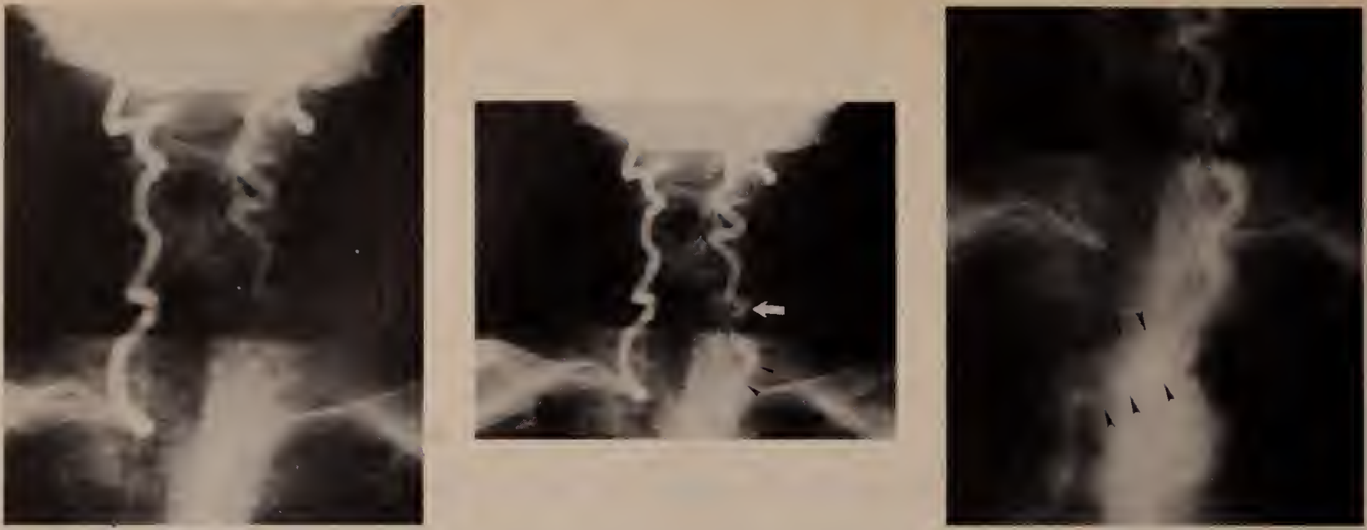

FIGURE 2. Left, selective right vertebral artery injection. Early film demonstrating flow up the right vertebral artery and reversed flow in left. Center, later arterial phase film demonstrating small pseudoaneurysm (large arrow) at site of fistula with vertebral vein (arrows). Right, left innominate vein opacified (arrows).

symptoms more closely simulated those associated with the subclavian steal syndrome. Perhaps the occlusion of the ipsilateral vertebral artery at its origin, in addition to the fistula, were responsible.

In this case, careful angiography provided for precise diagnosis facilitating the surgical repair.

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Long-term ultrafiltration as a treatment of refractory congestive heart failure

STANLEY MISLER, MD, PHD, BERNARD D. NIDUS, MD

Congestive heart failure is marked by expansion of extracellular fluid volume, which initially augments the function of the failing heart. Eventually, increased cardiac afterload,[1] cardiac dilation, and diminished cardiac output result, and edema and visceral congestion ensue. Diuretics, positive inotropic agents, and vasodilators are usually successful in reducing extracellular fluid volume and maintaining acceptable functional status.

We describe a patient with severe biventricular failure, refractory to pharmacotherapy, in whom successful treatment was centered on the removal of approximately 4 kg of plasma water by ultrafiltration as an outpatient, once weekly for nearly one year.

CASE REPORT

A 49-year-old bedridden man was admitted to the hospital for worsening heart failure and atrial fibrillation. He had a 25-year history of mitral valve disease treated by a commissurotomy and subsequent installation of a Starr-Edwards prosthesis. His therapy at home included digoxin, furosemide, warfarin, procainamide, bronchodilators, and low-flow oxygen. On physical examination, he was profoundly dyspneic at rest and was orthopneic. His blood pressure was 85/60 mm Hg; pulse, 100 to 110 beats/min and irregular; respirations, 30/min; and weight, 75 kg. Cardiac examination revealed distended neck veins, S_1 of changing intensity, prosthetic valve clicks, and a ventricular gallop sound. Rales and expiratory wheezes were heard in both lung fields. His liver was palpable to the iliac crest. His legs exhibited massive edema, to the point of oozing serous fluid.

Representative laboratory data were as follows: serum sodium, 125 mEq/L; potas-

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From the Division of Nephrology, Department of Medicine, New York University School of Medicine, New York.

Address correspondence to Dr Misler, Assistant Professor, Department of Medicine and Physiology, Division of Nephrology, The Jewish Hospital of St Louis, Washington University Medical Center, 216 S Kingshighway, St Louis, MO 63110; or Dr Nidus, Director of Hemodialysis, Renal Division, New York Veterans Administration Medical Center, 1st Ave at 24th St, New York, NY 10009.

sium, 3.5 mEq/L; carbon dioxide, 40 mEq/L; chlorine, 80 mEq/L; BUN, 70 mg/dL (25 mmol/L); creatinine, 1.2 mg/dL (106 mol/L); creatinine clearance, 45 mL/min; arterial blood gas pH, 7.39; PCO_2, 48 mm Hg; and PO_2, 49 mm Hg on 1 L of O_2 by nasal cannula. A chest roentgenogram showed increased anteroposterior diameter, cardiomegaly with four-chamber enlargement, pulmonary vascular congestion, and bilateral blunting of costophrenic angles. An electrocardiogram showed atrial fibrillation, a ventricular rate of 100 to 110 beats/min, right deviation of the electrical axis, and Q-, R-, S-, and T-wave changes consistent with right ventricular hypertrophy and a lateral wall myocardial infarction. Cardiac catheterization revealed left ventricular hypokinesis (cardiac index, 2.1 L/min), severe pulmonary artery hypertension (artery pressure 78/48 mm Hg, mean left atrial pressure 30 mm Hg) and an adequately functioning prosthetic mitral valve.

In the hospital, he was treated with stringent daily restriction of sodium (0.5 to 1 g) and fluids (≤800 mL). Digoxin was administered to the point of nausea, and it increased ventricular ectopy. Furosemide (200 to 300 mg intravenously twice daily) and ethacrynic acid (100 mg intravenously twice daily) reduced the serum sodium level to 120 mEq/L and caused a severe decrease in auditory acuity but resulted in no weight loss. Combined use of these diuretics and dopamine (4 to 5 mg/kg/hr intravenously) for 10 days resulted in less than 1 kg of weight loss. Trials of oral prazosin (1 mg three times daily) and oral hydralazine (20 mg four times per day) had to be discontinued because of a fall in supine blood pressure to 60 mm Hg, faintness, and chest pain. Attempts at electrical and chemical cardioversion to sinus rhythm were unsuccessful.

After four months in the hospital, with his status unchanged from admission, the patient underwent repeated ultrafiltration. Each procedure, lasting four hours, was performed using systemic heparinization, a blood pump at a flow rate of 125 to 150 mL/min, and a parallel-plate, 1 m^2, $11.5\text{-}\mu$ cuprophan dialyzer. The blood compartment was primed with saline, but no dialysate was used. The upper dialysate port was clamped, and the lower port was connected to a vacuum pump set to create a total transmembrane pressure of 500 to 650 mm Hg. Initial ultrafiltrations were performed via bilateral femoral vein cannulas; subsequently vascular access was achieved via a small arteriovenous fistula created at the wrist.

Table I demonstrates the physiologic effects of an early ultrafiltration. A total of 5 kg of fluid was removed at 1.5 kg/hr during the first two hours and 1 kg/hr during the remaining two hours. Standing blood pressure was nearly constant after ultrafiltration; supine and sitting blood pressures were 80 to 85 mm Hg throughout. Pulse rate remained at 100 to 110 beats/min throughout. The increase in PaO_2, the decrease in $PaCO_2$, and the fall in respiratory rate after ultrafiltration suggest that both ventilation-perfusion imbalance and overall ventilatory function were improved. The increases in hematocrit and serum albumin concentrations reflect a contraction of plasma volume. The constancy of serum sodium, creatinine, and urea nitrogen levels occurs because the ultrafiltrate and plasma have essentially the same concentration of small molecules that are not bound to protein.

TABLE I. Physiological Changes With Ultrafiltration

	Third Ultrafiltration		Long-term Ultrafiltration		
	Before	After	Before	After	(No. of Weekly Determinations)
Weight, kg	72.5	67.5	63.1–64.2	57.6–58.5	(4)
Systolic blood pressure, mm Hg	85	80	90–93	70–80	(4)
Respiratory rate, beats/min	30	22	20–22	12–15	(4)
PaO_2, mm Hg	55*	69*	56–58†	67–68†	(2)
$PaCO_2$, mm Hg	49	41	47–48	42–44	(2)
Vital capacity, L			1.2	1.65	(1)
Maximum midexpiratory flow, L/min			1.1	2.2	(1)
Hematocrit, %	30	42	38–43	48–50	(4)
Serum sodium, mEq/L	125	128	133–136	135–139	(4)
BUN, mg/dL	65	65	44–50	42–48	(4)
Serum albumin, g/dL	3.7	5.5	3.6	4.5	(1)
Serum creatinine, mg/dL	1.4	1.3	1.0–1.3	1.1–1.4	(4)

* Fraction of inspired oxygen = 24%.
† On room air.

After a total of four ultrafiltrations performed during three and one half weeks, he weighed 63.5 kg and had some leg edema, and could sleep in a supine position, walk 100 m, and climb one flight of stairs with minimal dyspnea. Cardiac ejection fraction was computed as 27% from a radionuclide ventriculogram. He became responsive to diuretic therapy, losing an additional 2 kg during the next three days. He was discharged from the hospital on therapy of 5 mg of warfarin, 0.25 mg of digoxin, and 120 mg of furosemide daily, and 10 mg of metolazone every other day. Once-weekly ultrafiltration, as an outpatient in a long-term dialysis unit, was instituted because he gained 4 kg during the next three weeks, despite attempts at salt and fluid restriction. He continually refused increased diuretic dosage (due to hearing loss) and new attempts at vasodilator therapy.

Table I shows physiologic parameters measured just before and immediately after ultrafiltration on four consecutive weekly treatments during the month of this therapy. His physical examination before treatment revealed a body weight of 63 kg, trace dependent edema with complete healing of the leg ulcers, absence of jugular venous distention, and decreased liver span. His dry weight was determined to be 58 kg, in that severe hypotension occurred when further fluid removal was attempted; infrequent asymptomatic bouts of hypotension (to 70 mm Hg systolic) and increased tachycardia (to 130 to 140 beats/min) during ultrafiltration responded to 100 mL of saline solution. Since the start of ultrafiltration therapy, his pretreatment respiratory rate had declined and PaO_2 on room air had increased, suggesting improved ventilatory function. Removal of 5 to 6 kg of fluid during ultrafiltration resulted in small but consistent increases in PaO_2 and vital capacity and decreases in $PaCO_2$ and respiratory rate. In addition, his BUN level had fallen, and his serum sodium level had risen, while his creatinine clearance remained fairly constant (range, 32 to 57 mL/min on four determinations), suggesting a reduction in prerenal azotemia and improved water excretion. He was now able to live independently and even drive to the seashore for fishing trips.

Figure 1 demonstrates daily urine volumes and sodium excretion after two successive weekly ultrafiltrations. Immediately after ultrafiltration, urinary sodium excretion was less than 10 mEq/24 hr, possibly reflecting transient reduction in plasma volume. On the next two days, a distinct diuresis and natriuresis occurred, with the urinary sodium level rising to nearly 90 mEq/24 hr. Thereafter, with continued diuretic therapy, there was a steady weight gain until the next ultrafiltration. During these two weeks, sodium intake calculated from weight gain and urinary sodium excretion averaged 140 mEq/day. The patient failed to further restrict his sodium intake at home.

After nine months of weekly ultrafiltration, he began to exhibit progressive deterioration marked by episodes of tracheobronchitis, increasing dyspnea, weakness, peripheral cyanosis, and rising BUN level despite unchanged PaO_2, serum creatinine clearances, or preultrafiltration weight, and edema. One year after his first ultrafiltration, he was admitted to the hospital with extensive bowel infarction and he later died. An autopsy was not performed.

DISCUSSION

Extracorporeal ultrafiltration provides a means for rapid reduction of intravas-

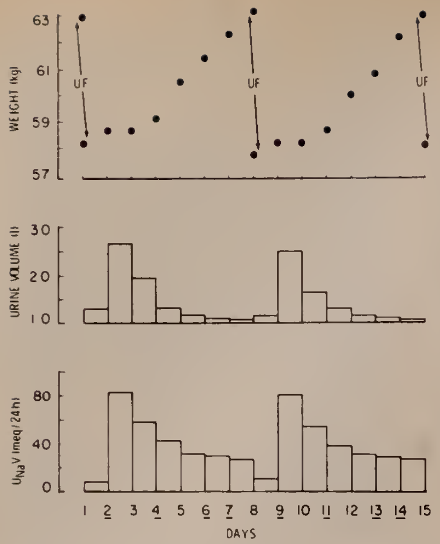

FIGURE 1. Daily weight, urine volume, and sodium excretion during 15-day period during seventh month of weekly ultrafiltration (UF). Patient received 120 mg of furosemide daily and, on days underlined, additional 10 mg of metolazone.

cular volume. The flow of blood past a membrane of small pore size, across which a pressure gradient exists, results in a movement of water and small molecules from blood into the surrounding lower-pressure compartment. Filtration of water and small solutes from plasma increases plasma oncotic pressure.[2] Reduced plasma volume diminishes capillary hydrostatic pressure that, together with increased plasma oncotic pressure, favors the movement of water and solute from extravascular pools into the intravascular space.

Single ultrafiltration treatments have been used in the treatment of pulmonary edema with or without accompanying oliguria.[2-4] Short courses of intermittent ultrafiltration (one to four times) have been used to remove excess fluid in patients with nephrotic syndrome, cirrhosis, or congestive heart failure, who thereafter improved and became responsive to diuretics.[4-6] Continuous ultrafiltration has been used in oliguric, fluid-overloaded patients with progressive azotemia.[7] Modest ultrafiltration of several liters effects a substantial reduction in pulmonary capillary wedge pressure as well as a small to moderate reduction in cardiac output,[2,8] but has little effect on systemic blood pressure, perhaps because it does not hinder effective compensatory increases in the plasma catecholamine and renin activity that maintain vascular tone.[9] The latter may have contributed to this patient's better physiological tolerance of ultrafiltration compared to pharmacologic unloading.

The experience with this patient suggests that intermittent ultrafiltration can be used on a long-term basis in patients with refractory congestive heart failure and borderline hypotension but nominally adequate renal function to achieve sustained reductions in edema and organ congestion, increased ventilatory function, and improvement of hyponatremia and prerenal azotemia. We have no evidence that this therapy altered the course of the myocardial disease, especially as the patient's course was suggestive of a progressive, low cardiac output and peripheral hypoperfusion. The mechanism of postultrafiltration diuresis and natriuresis, whether secondary to an increase or redistribution of renal blood flow or otherwise, as well as the long-term hemodynamic effects of repeated ultrafiltration are worthy of more detailed study.

The cost of each four-hour ultrafiltration (nurse's salary plus disposable materials) was estimated to be less than $100, thus making weekly outpatient ultrafiltration therapy for one year less expensive than hospitalization for one month in a general medical ward.

Long-term extracorporeal ultrafiltration carries with it a series of potential problems. The risks of air embolism, blood loss, thrombosis, and the requirement for long-term vascular access, which might worsen heart failure, are endemic to any procedure that requires extracorporeal circulation. Long-term intracorporeal ultrafiltration could be performed by the instillation of hypertonic dialysate into the peritoneal space via an indwelling peritoneal catheter. The latter procedure would replace the risks of extracorporeal circulation with the risks of peritoneal dialysis. There is a risk of profound intravascular volume depletion and hypotension, particularly in patients with massive ascites or pleural effusions, as well as acute hemoconcentration with either method of ultrafiltration.

This patient was treated before the availability of the newer, more potent vasodilators such as captopril. The improvement in the patient's functional status, however, did continue without obvious complications for several months. Given the toxic reactions and tachyphylaxis that can occur with available drug therapy for refractory heart failure,[10] intermittent ultrafiltration may be a reasonable short-term therapy for selected individuals, while a stabilizing pharmacotherapy regime is being developed or prior to cardiac surgery or transplantation. Ultrafiltration may deserve further consideration as a long-term therapy when complex pharmacotherapy has proven less than optimal.

Acknowledgment. The New York Veterans Administration Medical Center dialysis staff and physicians at the New York University School of Medicine, New York City, participated in the care of the patient.

Cleveland Symonette and Helen Odle provided secretarial assistance in preparing this article.

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Distal kinking of a pulmonary artery catheter as a cause of fatal hemoptysis

ROBERT D. BRANDSTETTER, MD, NASIR ALARAKHIA, MD, LORRAINE COLI, MD,
BERNARD GITLER, MD

Hemoptysis following pulmonary artery catheterization is being reported with increasing frequency.[1-10] Several explanations have been proposed for the catastrophic hemorrhage that may occur.[2,4,5,9,10] The use of lateral chest roentgenograms to document the position of the catheter within the West zones of the lung has been reported.[11] We describe a case of fatal hemoptysis in which the lateral chest roentgenogram documented catheter distortion as a factor contributing to this fatal event.

CASE REPORT

A 75-year-old woman with diabetes mellitus was admitted to the intensive care unit because of an intra-abdominal abscess and *Klebsiella* sepsis. She was started on broad-spectrum antibiotics and was taken to surgery for emergency laparotomy. A Swan-Ganz catheter was inserted into the right internal jugular vein in order to monitor hemodynamics. The pulmonary artery catheter was positioned without difficulty, and appropriate pressure tracings were obtained. The pulmonary artery pressure was 30/17 mm Hg and the pulmonary capillary wedge pressure (PCWP) 16 mg Hg. Anteroposterior (Fig 1) and lateral chest roentgenograms were obtained demonstrating satisfactory placement. At surgery, a ruptured liver abscess was found and evacuated. Upon return from the operating room, repeat anteroposterior and lateral roentgenograms were obtained to re-evaluate the position of the catheter (Fig 2). The distal catheter tip was noted to have migrated peripherally and was therefore withdrawn approximately 3 cm. Following this withdrawal, a dampened PCWP tracing was obtained. The catheter was flushed, no further inflation of the balloon was attempted, and a third set of roentgenograms was obtained that showed the catheter to be peripherally located. With the balloon still deflated, the catheter was again pulled back gently one hour after noting the dampened PCWP tracing. Shortly thereafter, the patient had fatal hemoptysis. Permission for autopsy was not obtained. A more careful review of the last two roentgenograms (Fig 3) revealed a kink in the distal tip of the Swan-Ganz catheter, which presumably precipitated trauma and was the cause of the patient's massive hemorrhage.

DISCUSSION

Fatal hemoptysis following pulmonary artery catheterization has been considered to be secondary to several mechanisms in which vascular perforation may occur:[2,4,5,9,10] the inflation and deflation of the balloon can disrupt the artery, eccentric or distorted balloon inflation can push the catheter tip through the vessel wall, or the catheter tip can advance too far peripherally and cause perforation. The occurrence of a large catheter loop in the right ventricle can set the stage for migration of the catheter.[10] Pulmonary hypertension has been implicated when the elevated pressure distends the arterial vessels and causes the catheter to become lodged more peripherally than when the pulmonary artery pressure is normal.[5] Finally, the increased pressure gradient from the pulmonary artery to the pulmonary wedge during balloon inflation may cause the catheter to advance peripherally.[9] Anticoagulation, increased age, and excessive catheter manipulation have also been associated with higher risks of pulmonary artery hemorrhage.[9]

We present a case of fatal hemoptysis with a lateral roentgenogram that illustrates a possible cause for pulmonary artery rupture. Review of the lateral roentgenogram (Fig 3) demonstrated a kink in the distal tip of the catheter that was not visualized on the anteroposterior roentgenogram (Fig 2) and was not initially identified on the lateral roentgenogram. Because of the unacceptable peripheral location, the catheter was slowly withdrawn with the balloon deflated. The final anteroposterior roentgenogram, obtained just before death, demonstrated shortening of the catheter loop in the right ventricle (compared to Fig 2) and no proximal movement of the distal kinked catheter tip. It appeared as though the distal tip was snagged. Tightening of the right ventricular catheter loop has been reported with the catheter sutured on the skin, thereby indicating further distal migration of the catheter.[7]

It is possible that a combination of effects may have resulted in acute pulmonary artery rupture in this patient. The catheter tip either migrated or was advanced too far peripherally.[1] Perforation and lodgment of the catheter tip may have occurred at this time, with hemorrhage occurring later as the catheter was withdrawn. This seems unlikely, however, since several hours elapsed after the first withdrawal of the catheter, and there was no associated hemoptysis. Another possibility is that the catheter lodged up against a distal vessel and bent on itself, with spontaneous migration, and upon withdrawing it on two occasions, disruption of the arterial wall occurred. A third alternative is that with the first withdrawal the catheter kinked on itself, as supported by the dampened PCWP wave form. A further attempt at withdrawing the catheter was followed by fatal hemoptysis.

Unlike previously reported episodes of pulmonary artery rupture in which the catheter spontaneously migrated[10] or was being advanced,[8,9] or the balloon was being inflated,[6] this may be the first case in which fatal hemorrhage resulted following withdrawal of the catheter. How often kinking of the distal tip of flow-directed catheters occurs is unknown, since lateral roentgenograms are not routinely performed. In a study by Shasby et al of 30 patients,[11] none of the catheters was noted on lateral roentgenogram to have a kink. In a series of 74 patients in this institution, only one catheter had a kink. Whether these catheter defects straighten spontaneously is also speculative. It does appear that the more peripheral the catheter migration, the greater the probability of

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From the Department of Medicine (Drs Alarakhia and Coli), the Divisions of Pulmonary Medicine (Dr Brandstetter) and Cardiology (Dr Gitler), New Rochelle Hospital Medical Center, New Rochelle, New York.

Address correspondence to Dr Brandstetter, Assistant Director, Department of Medicine, New Rochelle Hospital Medical Center, 16 Guion Place, New Rochelle, NY 10802.

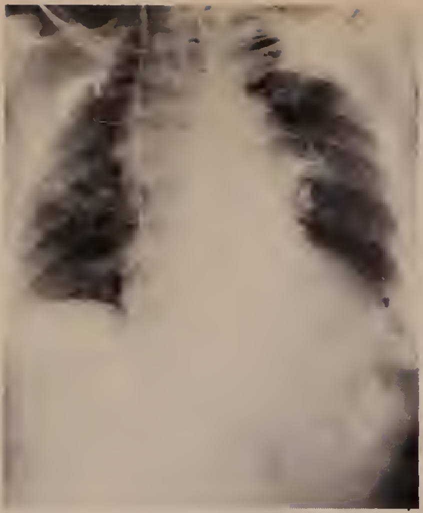

FIGURE 1. Anteroposterior roentgenogram demonstrating satisfactory placement of Swan-Ganz catheter.

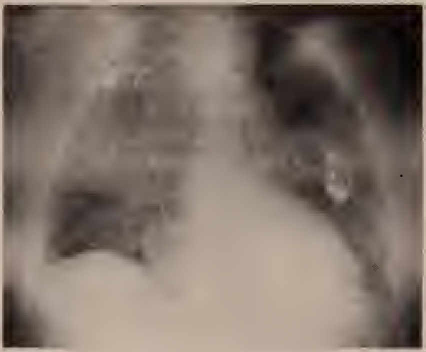

FIGURE 2. Anteroposterior roentgenogram demonstrating peripheral migration of tip of Swan-Ganz catheter.

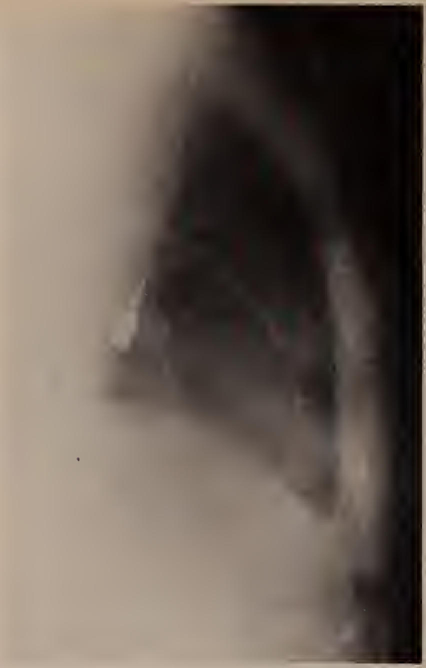

FIGURE 3. Lateral roentgenogram demonstrating kink in catheter tip and large right ventricular catheter loop.

kinking as smaller end vessels are entered.

Although the original guidelines for use of the balloon-tipped catheter by Swan and Ganz[12,13] should be adhered to, we agree with Foote et al[7] that one should avoid advancing the catheter once the initial PCWP recording is obtained. In addition, no catheter tip should remain in a position with a dampened pressure tracing. Additionally, frequent roentgenograms should be obtained to ascertain tightening of the catheter loop in the right ventricle suggesting further peripheral migration of the distal tip.[10] We strongly recommend that in addition to anteroposterior films in all patients with pulmonary artery catheters, a lateral roentgenogram should be obtained when the catheter tip is noted to be too peripheral. This is not obtained merely to assess the catheter's anatomic position within the lung, but rather to identify any unusual configuration that may be dangerous and not apparent on a routine anteroposterior film. In addition, if the catheter requires multiple manipulations, it is conceivable that the use of fluoroscopy may identify distorted catheters not visualized on anteroposterior or lateral roentgenograms. Such visualization may allow safer manipulation of these catheters under such conditions.

In conclusion, this may be the first report of distal kinking of a flow-directed balloon catheter wedging within either tissue or a small pulmonary artery. We cannot recommend blind withdrawal of the catheter when this finding is noted. Fluoroscopic examination may better define the distal tip and, should parenchymal or arterial extravasation or both be noted on withdrawal, embolization through the same catheter may reduce hemorrhage.

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Health care in Nicaragua: a social and historical perspective

EMORY M. PETRACK, MD

The controversy surrounding Nicaragua continues to be a major focus of the mass media. Over the past several years, much has been written about reported advances in health care in this poor, Central American country. As a fourth-year medical student concerned with issues of public and international health, I visited Nicaragua, observing and studying firsthand some of the ongoing changes in health care.

Although many North Americans are aware that in July, 1979 the Sandinista Front for National Liberation (FSLN) overthrew the Somoza regime, fewer are probably familiar with the roots of the Nicaraguan revolution. To appreciate the advances in health care since 1979, it is useful to examine them within a historical framework.

THE SOMOZA REGIME

Almost continuously from 1909 to 1933, Nicaragua was occupied by United States marines.[1] In 1933, their withdrawal left in power the United States-backed National Guard and the first dictator, Anastasio Somoza Garcia. The successive regimes of Somoza Garcia, and his son, Somoza Debayle, became known throughout the world for their repression and brutality against the Nicaraguan population. The 1972 earthquake in the capital city of Managua killed 20,000 people and destroyed much of the city. Many observers believe that Somoza diverted the international funds for the reconstruction of Managua to his family and National Guard officers.[1] By 1979, the Somoza family was estimated to be worth nearly one billion dollars, and to control 60% of the national economy and 25% of the arable land.[1] The economy was controlled by the National Guard.

Health conditions under the Somoza regime are difficult to evaluate, for lack of data and underreporting were the norm. Life expectancy was reported to be 53 years, and the infant mortality rate was estimated to be between 120 and 146 per 1,000 live births.[2] As in many Third World countries, preventable diseases were the principal causes of death. Infectious diseases, diarrhea, and dehydration accounted for almost one third of all deaths and over 50% of infant mortality. Two thirds of children under five experienced some degree of malnutrition.[2]

The health care system under Somoza was administered by 23 separate agencies, including the National Social Security Institute (INSS), a national Ministry of Health, independent local health ministries, and autonomous public hospital governing boards. While the INSS provided services that consumed about 40% of the total health sector expenditure, it served less than 10% of the population—mostly persons with secure jobs who lived in the larger cities.[3] More than 50% of the people lived in rural areas, yet there were few services for this portion of the population. Managua, the largest city, was home to 25% of the population, but 50% of the doctors and 75% of the professional nurses. There was little commitment to maternal and child health, even though 50% of the population was under 15 years of age.

In 1962, the FSLN started an armed movement to overthrow the Somoza dictatorship. In 1978, they united a substantial proportion of the population behind a national insurrection against Somoza and the National Guard. The Federation of Medical Societies of Nicaragua participated in hospital strikes led by FETSALUD, the non-physician health workers' union. The Nicaraguan people organized themselves into hundreds of Civil Defense Committees (CDCs). These CDCs formed the embryo of the future Sandinista Defense Committees, through which massive participation in restructuring post-war Nicaragua would take place.

On July 19, 1979, the dictatorship was overthrown by the popular uprising. But the war had taken a great toll on the country. Of a population of 2.7 million, 50,000 were killed, 100,000 wounded, and 40,000 children orphaned. Many production sites were destroyed, as were many health care facilities. Somoza left behind a foreign debt of 1.6 billion dollars, which the FSLN needed to honor in order to qualify for drastically needed loans. It was in this context that the people of Nicaragua set out to reconstruct their war-torn society.

HEALTH CARE TODAY IN NICARAGUA

Following the defeat of Somoza, the new government faced the immediate problem of how to care for the tens of thousands of persons wounded, and how to distribute the aid and medical supplies coming in from other countries. As with the fight against Somoza, the key to achieving these tasks was popular participation and organization. It was a

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Address correspondence to Dr Petrack, Residency Program in Social Medicine, Division of Pediatrics, Montefiore Hospital and Medical Center, 3412 Bainbridge Avenue, Bronx, NY 10467.

The author spent six weeks during July and August, 1983, as a health-care worker in Nicaragua. This overseas program was undertaken as part of a fourth-year elective in the Department of Preventive Medicine and Community Health at the State University of New York, Downstate Medical Center, Brooklyn, NY.

question of shifting energy from military activity to the task of reconstruction. The Civil Defense Committees, still intact, were converted to Sandinista Defense Committees (CDSs), encompassing all sectors of the population—men and women, workers and peasants, urban and rural inhabitants.

Currently, more than 25% of the Nicaraguan population is active in the CDSs, which function at local, regional, and national levels. Their role, in addition to local defense, includes direct participation in education, food distribution, and health education and services. In addition to the CDSs, other forms of popular participation include the Nicaraguan Women's Association, the workers' unions, and youth organizations. The Popular Health Councils, which help with local and regional health planning, draw their members from each of the other groups.

It was through these organizations that the Emergency Campaign was launched (Belmar R, Fox J, Solimano G: *Health in Nicaragua: Two Years After the Revolution*, unpublished report). By March 1980, the following was accomplished: (1) 200 oral rehydration units were created to treat diarrhea and dehydration in children; (2) an emergency nutrition program was created, aimed at children and pregnant and lactating women; (3) more than one million doses of polio, measles, DPT and BCG vaccines were given to children five years of age and younger; (4) 250,000 pediatric visits were recorded; (5) 8,000 new latrines were installed; and (6) 500 maternal and child health auxiliaries were trained, with emphasis on the management of diarrhea.

By the early part of 1980, the new government was addressing more directly the organization of the health care system. Unlike the fragmented services under Somoza, health care in the new Nicaragua fell under the control of a unified Ministry of Health (MINSA). MINSA was responsible for the operation of the Unified National Health System (SNUS), created with these stated goals: (1) to provide adequate health care to all individuals without distinction of social class; (2) to expand the health services throughout the country and to develop programs to control the most prevalent diseases; and (3) to actively incorporate the community and popular organizations into the planning and implementation of health programs.[4]

In 1980, the FSLN initiated an intensive campaign against illiteracy. One hundred thousand young Nicaraguans, called *brigadistas*, were trained and sent around the country to teach basic reading and writing. Through this effort, illiteracy (defined as reading and writing below the third grade level) was reduced from 50% to 13%.[5] In addition, 1 out of 10 *brigadistas* was trained in elementary health principles. They were responsible for educating others about hygiene and basic sanitation, as well as for distributing anti-malarial medication.

Five Popular Health Campaigns were waged during 1981 against polio; measles, diphtheria, pertussis, and tetanus; rabies; poor sanitation; and malaria.[3,5,6] Whereas overall planning and technical support was provided by MINSA, the popular organizations in each region were encouraged to develop their own strategy to improve local conditions and resources. An estimated 85% of children under five years of age were vaccinated against polio, and by 1984, almost 90% had been immunized against measles.[3] While dramatic improvement was seen in each issue addressed, the campaign against malaria and dengue fever exemplified the Nicaraguan people's increasing organizational capacity. This campaign began with a nationwide effort to clean up potential breeding sites of the mosquito vectors. Then, in November 1981, 80,000 trained volunteers distributed anti-malarial drugs in a one-time, three-day exercise, reaching about 75% of the population. The result was a dramatic (98%), although temporary, decrease in the incidence of malaria one month later.[5,7]

Since women and children comprise about 75% of the population, maternal and child health is a priority. Emphasis has been placed on prenatal care and education, and the number of births attended by trained health-care workers has been steadily increasing. Most births, however, still occur outside of appropriately equipped health-care facilities. A program has been established to promote breast-feeding and to improve childhood nutrition.

Diarrhea and dehydration have continued to be a major cause of morbidity and mortality in children. The Sandinistas' approach to this problem has been the creation of over 200 oral rehydration units (UROs).[4,5] The purpose of these units, in addition to the oral replacement of an appropriate salt and glucose solution, is to educate health-care workers about the prevention and treatment of diarrheal disease. Dissemination of information and educational materials is accomplished through the popular organizations, such as the Nicaraguan Women's Association. In the first 21 months of the program, 92,000 children were treated in UROs. Eighteen percent of those treated had serious dehydration (5 to 10%) and another 2% had grave dehydration (more than 10%). Only 2.6% required intravenous therapy, and only 17 infants, or 0.02% of those treated, died.[5] This program has been an important factor in the reduction of infant mortality, currently 82 per 1,000 live births.[8]

The education of health-care workers has also been a priority. Before 1979, auxiliary nurses and health technicians received little or no training. Since that time, a polytechnical institute has been created, educating students in many important fields such as laboratory and x-ray technology. The number of trained nurse auxiliaries has tripled, and the number of nursing and medical students that graduate each year has increased more than fivefold.[3]

Although there have been many positive changes in Nicaragua, there are potential problems with this new system of government. The popular organizations, which help to plan and provide essential services, are also used to generate support for the government's policies. Although these organizations clearly encourage popular participation, their influence is sometimes exaggerated by the Sandinistas.

With regard to health care, there is a chronic shortage of supplies and personnel, and capital to build new facilities. With increased access to health services, there has been a concomitant increasing strain on the system, resulting in overcrowded clinics and shared beds in hospitals. Supplies that were meant to be disposable, such as surgical gloves, are cleaned and reused. These difficulties reflect the current state of transition in the health care system.

FOREIGN AID

International aid has been very important to health care.

Many organizations, such as United Nations International Children's Educational Fund (UNICEF), Oxfam, the Organization of American States, the European Economic Community, the World Health Organization (WHO) and the Pan American Health Organization, have helped substantially. In 1982, UNICEF/WHO awarded Nicaragua its annual prize for the greatest achievements in health by a Third World nation. Medical supplies and personnel have arrived from more than 24 countries, much of them from Western Europe and Latin America. Although the United States government does not send aid to Nicaragua, many American doctors and other health workers have sent materials privately. In November 1983, the first United States-Nicaraguan Health Colloquium was held in Managua. It involved 120 American and Canadian health workers from 48 cities, as well as 600 Nicaraguan physicians, nurses, midwives, technicians, and *brigadistas;* the colloquium was endorsed by the Pan American Health Association and the American Public Health Association. There was an exchange of information through papers and workshops; the United States delegation brought an estimated $60,000 worth of medical equipment, books, and journals. The second United States-Nicaraguan Health Colloquium was to be held in Managua this month.

THE UNITED STATES AND NICARAGUA

As I traveled around the country, I had the opportunity to speak with many Nicaraguans about their concerns for the health care system. People were quite open about discussing the particular health-related problems in their community, including lack of health-care workers and facilities, long lines, and, sometimes, mismanagement of supplies.

Two common themes emerged during my travels. On the one hand, there was a general recognition and appreciation by the people of the many positive changes in the delivery of health services. The Sandinista government was recognized and appreciated as a major force behind the advances made nationally and on the local level. On the other hand, there was a widespread understanding of the negative impact that United States-backed attacks against Nicaragua have had on their health care system.

As physicians concerned with the improvement of health services, we should be concerned not only with the curative and preventive side of health care, but also with the social, economic, and political aspects of society that influence health and disease. It has become clear that the United States is attempting to destabilize and even overthrow the Sandinista government. The money the government of Nicaragua uses to defend itself against this interference is money that is needed to improve not only the health care system, but the entire social and economic infrastructure.

The previous decades of United States influence in Nicaragua cannot easily be forgotten, for they include a history full of pain, suffering, and death for the Nicaraguan people. They are now living under a government that is committed to improving the life of the average Nicaraguan; they are seeing more health centers, more housing, better education, and agrarian improvements. A national food program has been launched to achieve self sufficiency in the production of basic foodstuffs. Their children are surviving longer. In short, the very social fabric of Nicaraguan society has improved markedly for the majority of the people. Diverting funds away from Nicaraguan destabilization and toward social needs here in the United States would have a positive impact on health services for both the Nicaraguan and the American people.

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ESSAY REVIEW

The Clinical Consultations of Giambattista Morgagni

The Edition of Enrico Benassi (1935)

Translated and edited by Saul Jarcho, MD. *536 pp. Charlottesville, The University of Virginia Press, 1984. $42.50 (hardcover)*

A few lines of introduction about the founder of the discipline of pathologic anatomy, whose name is one of the glories of Italian science in the 18th century, may be useful to form an image of the man before reading about his work.

Giovanni Battista (or Giambattista) Morgagni, born in 1682 in Forli, received his medical degree at the age of 19 in Bologna, where he was the favored pupil of Valsalva. He then went to Padua and Venice to continue his studies, but returned to Forli where he began his medical practice. At the age of 29 he accepted an offer of the chair of anatomy at Padua and held this position for 56 years. He died at the age of 89, having fathered 15 children. His greatest achievement was the establishment of a close link between anatomy, pathology, and clinical medicine. His major and best known work, *De Sedibus et Causis Morborum per Anatomen Indagatis* (*On the Sites and Causes of Diseases Revealed by Anatomy*), was printed in five volumes in 1761 when Morgagni was 79. This masterpiece of knowledge and experience gives detailed histories of illnesses and related pathologic findings seen on autopsies of nearly 700 people. The list of morbid conditions described by Morgagni is astonishing; it comprises acute yellow atrophy of the liver, syphilitic aneurysms, pneumonia, cancer of the stomach, endocarditis, mitral stenosis, meningitis, tetralogy of Fallot, cerebral gummata, and many other entities. The anatomic discoveries of Morgagni are reflected in a dozen eponyms, known to every student of medicine. The Latin text of this work was translated into English by Benjamin Alexander, MD, an Irish physician; it was published in 1769 and reprinted twice in 1960 and 1980, under the auspices of the New York Academy of Medicine.

But Morgagni was not only a busy "morbid anatomist," a sort of ghoul of the morgue, given to the dissection of dead bodies. He was also a historian, a philosopher, an experimenter and a good clinician. The latter aspect of Morgagni's personality is less known, for reasons that are well explained by Saul Jarcho, MD, in his preface to *Clinical Consultations*. The original Italian edition of *Clinici Medici*, prepared by Enrico Benassi, was published for the first time 164 years after the death of its author. This alone is a fascinating story!

Shortly before he died, Giambattista Morgagni selected for his pupil Michele Girardi a series of letters on clinical consultations given to various persons. These papers were a small part of 12 volumes of other unpublished writings of the master. When Girardi died in 1797, these records were acquired by the Duke of Parma and stored in the cellars of the Palatine library, where they were virtually untouched for over a century. It was not until 1935 that this series of letters, written in flowery and convoluted Italian with many erasures and corrections, was edited under the title *Consulti medici*, annotated by Professor Enrico Benassi of the University of Turin and published in 500 copies by Capelli of Bologna. Full recognition of the value of this book was slow to come, but medical historians have now become aware of the exceptional interest of this scholarly work, as a source of information on Italian medicine of the period and as testimony of Morgagni's clinical activity.

No one would have been better qualified to render this gem of medical history into English than Dr Jarcho, whose prestige as an erudite researcher and writer stands very high. This handsome volume opens with a brief introduction by Jarcho, followed by the translation of Benassi's foreword to the 1935 edition. The next 50 pages comprise a learned preface by Jarcho, who has been studying Morgagni's work since 1948. He presents the historic background of the publication and traces the then dominant currents of opinion on the etiology and pathogenesis of diseases. They were based on doctrines of humors and particles, with concurrent influence of meteorologic factors, and are reflected in Morgagni's philosophy of somewhat skeptical eclecticism.

The main part of the book consists of the description of 100 consultations that dealt with people from many strata of society and with a variety of illnesses or complaints: old wounds or ulcers, tumors of bone and flesh, diseases of lungs and kidneys, flaccidity of the penis, dyspareunia, difficult births, epilepsy, hemorrhoids, chronic gonorrhea, vaginal discharge, syphilitic gummata, asthma, scrofula, ozena, scabies, hypochondria, and others. Nearly every case history describes the patient and his symptoms, mentions the presumed causes, quotes the views of other physicians, recommends treatment, and often ventures to predict the likely outcome. The advice given by Morgagni displays attention to detail, clinical acumen, extensive reading, and the sympathetic attitude of a kind and wise physician. The treatments advised by Morgagni consisted of a range of plants and substances of vegetable nature, but also concoctions from vipers, dietary prescriptions, and hygienic measures—all supposed to have an influence on blood volume, body fluids, muscular tonus, and digestive action. With surgical problems Morgagni was prudently conservative. Morgagni's consultations did not always concern his own patients, but were often given to persons referred to him through correspondence with other physicians or various influential persons. This makes the *Consulti Medici* professionally less convincing than his earlier publication. Nevertheless, the gallery of human types and their illnesses is just as fascinating. The literary style of the Italian text of *Consulti Medici* was highly praised by Benassi, and yet it is obvious that parts of it were of "serpentine sinuosity" and not easy to render into readable English. Nevertheless, Jarcho succeeded brilliantly in giving it a lucid and elegant form, well adapted to the period.

The main part of the book is followed by three appendices, one of which provides a list of names of plants quoted in the text and their modern botanical equivalents. The final chapter consists of about 100 pages of notes and comments and remarks by Benassi and by Jarcho. The variety of these annotations, covering art, history, literature, botany, chemistry, and other aspects of knowledge is astounding; all are informative, although a few appear to be arch or abstruse. A list of 300 references and two indices of names and subjects complete the book.

This beautifully printed and well-bound volume represents a labor of love of a distinguished medical historian and will be of immense value to anyone interested in the state of medial science and clinical practice in 18th century Italy. It also reveals many little known aspects of the life and work of one of the prominent and attractive figures in the history of medicine. Any greater praise would be superfluous.

LEONARD JAN BRUCE-CHWATT, MD
Emeritus Professor of
Tropical Hygiene
University of London
Wellcome Museum of Medical Science
London, England

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EFFECTIVE USE OF AUTOPSY IN MEDICAL EDUCATION

Pathology is not a fundamental, basic science in the sense that physics and chemistry are. Yet clinical medicine is still further removed from this goal of ultimate understanding. It should be noted that physics and chemistry, too, will ultimately be written in terms of pure mathematics applied to the nucleus of the atom with its included smaller particles and the satellite electrons of the molecule. In a sense, biochemistry, microbiology, pharmacology, and physiology represent useful compromises with the "pure and fundamental" theory, necessary for understanding, in the present imperfect state of knowledge. Pathology represents a similar compromise at a lower level of the fundamental, yet it is justified fully by its more direct, ready application to medicine, whose plane of understanding is, as noted, at a still lower level of the fundamental and the absolute.

Pathology is a bastard offspring, born when the "parents," modern basic sciences, were unknown. It is an admixture of genes from all of them. Yet, it is this very impure background that is its source of strength as an instrument of integration and correlation. It is often necessarily descriptive only, and, oftener than not, it gives no numerical data easily subject to statistical analysis. It acquired a legitimate status only on the basis of pragmatic necessity in medical education.

The autopsy is a crass and crude investigative instrument compared to the flame photometer, the infrared or mass spectrometer, or the electron microscope. Its concepts are quite unrefined when compared to electron shifts and enzyme thermodynamics. Its usefulness still depends upon interpretative skill, and its technique in this respect approaches an art in its dependence on the intuitive and its lack of mathematic quantitation. Its range of error is much wider, to be sure. Yet, the autopsy offers the perfect setting for the pragmatic application of basic knowledge and helps materially by the orientation it affords to the practitioner of medicine. Without the autopsy as a means of discipline and control, the basic scientific knowledge, no matter how profound, can often be applied in medicine by post hoc association only.

The contribution of the basic sciences to the remarkable recent advances in medicine is obvious. Yet, it is from the mutable, variable interaction of all factors in the host as a whole, as seen at the autopsy, that the fullest measure of understanding of disease in the human can be elicited. The facts of basic science can be applied only superficially, if isolated from a comprehensive understanding of the whole disease process in the host as a whole. Good medical practice with accurate diagnosis and good clinical therapy require far broader, more complete comprehension than that of etiology alone. If the basic science contribution is applied as an isolated discipline in the interpretation of disease, the correlation can be only partial. Such contributions in basic science, if treated alone, without regard to the many other factors that enter into the complex picture of illness and pathology, must be one-sided and often lopsided. The changes wrought in each host vary, and a knowledge and understanding of these changes is essential for the larger appreciation of the full range of reaction of the disease process and its conceptual evaluation and clarification.

The application of the best scientific factual knowledge can be quite unscientific indeed, and on occasion may be only one step removed from quackery. One need hardly be a qualified, trained physician to administer a potent antimicrobial agent to a child with epidemic cerebrospinal (meningococcic) meningitis or to an adult with tuberculosis. It is the understanding of the etiology and the pathology, including the step-like stages in the pathogenesis and the complications, that makes the application of the basic science knowledge truly scientific from the medical standpoint.

ALFRED A. ANGRIST, MD
(*JAMA* 1956; 161:305)

THE ETIOLOGY, CONCEPT, AND PROPHYLAXIS OF CHILDBED FEVER

By Ignaz Semmelweis, MD. Translated by K. Codell Carter. 263 pp. Madison, WI, The University of Wisconsin Press, 1983. $10.95 (softcover)

K. Codell Carter's translation of Semmelweis' medical accomplishments illuminates the tribulations of this great contributor to science and his stormy relationship with the medical community.

The introduction constitutes about one fifth of the paperbook, but it serves well to highlight the essential points of Semmelweis' life and times. He was born and raised in Hungary. In the course of his studies, he made a sudden change from law to medicine, later specializing in obstetrics in Vienna. Carter describes a doctor who was prickly and dogmatic and none too popular among his colleagues. But he was committed to his field and exceptionally observant. He tackled a problem of monumental importance: Childbed fever was killing thousands of young women each year in Europe. And, unlike wars or epidemics, it was a constant threat.

Medical science was booming. Major discoveries were frequent, creating professors of almost unassailable stature and equally ballooned egos. They carved out their fields, and upstarts, especially ones with not very impressive credentials like Semmelweis, had best ask before they enter and then tread lightly.

After his first report in 1847, it became begrudgingly and belatedly clear that with Semmelweis' antiseptic methods, mortality due to puerperal fever could be reduced from about 20% to about 1%. Semmelweis proved this during his first and second clinics at a Viennese maternity hospital. This, as Carter indicates, had an impact on medicine comparable to Jenner's cowpox innoculation procedure for smallpox vaccination. What made Semmelweis' contribution so unique, as Carter elucidates, is that it dispelled "pathological anatomy" as an explanation for puerperal fever, and by extension, for all infectious diseases. And, it brought forth the modern etiological characterization of infectious disease.

This theoretical innovation shook the medical community to its very core. It also debunked too many important professors for Semmelweis' own good. But the fact that his theory explained so many confusing disease states, and that its clinical application—antiseptic patient care—was so successful has, over the years, elevated Semmelweis to the status of a true founder of modern medicine and surgery.

He had produced the "theory of relativity" for infectious disease. It awaited Koch, Pasteur and others to describe the "particles." And, like Einstein's theory, it has stood the test of time. Every day when doctors wash their hands—indeed Semmelweis, as Carter mentions, may have been the first to use the scrub brush—they are in fact paying tribute to this often misunderstood obstetrician.

K. Codell Carter's book is a superlative and enlightening account of Semmelweis' genius.

DONALD J. MOORE, MD
Torrey Pines OB-Gyn
Medical Group
Solana Beach, CA 92075

WE GAVE BIRTH TOGETHER: COLOR PHOTOGRAPHS AND DIALOGUE OF THE WORK, THE JOY, AND THE EMOTIONS OF CHILDBIRTH

By Karen Michele and Elisabeth Bing. 125 pp, illustrated. New York, William Morrow and Company, 1983. $15.95 (hardcover)

This is a straightforward and simply constructed book that documents with photographs and text the childbirth experiences of four couples. They convey their thoughts, feelings, actions and interactions during labor and delivery and the immediate postpartum period. More technical discussions appear in smaller print, contributing information related to the accompanying photographs. The topics covered include Lamaze techniques, fetal heart rate, posterior presentation, amniotomy, episiotomy, rotation, lateral delivery position, characteristics of the newborn, linea negra, contractions after birth, and nursing.

Contributing to the variety of the birth experience, there were couples expecting their first child and those delivering their second. Two couples had an additional support person besides the husband. In one case, the additional support was for a young sibling who was present at the delivery. The reactions to labor ranged from a mother who had a constant need to be held and encouraged, to another who did not like to be touched at all. One mother dealt with difficult contractions by rocking, another was distracted by her toddler. One baby that was not cooperating was pushed down by a squatting mother, aided by the father's strength. A 10-pound 1-ounce baby was delivered by a screaming mother in the Sims position. One mother, who was a nurse and had attended women in labor who lost their control, was particularly concerned about her own composure.

The husbands were present and actively participated in all four deliveries. Even the husband of the woman who did not like to be touched while in labor was called into active and appreciated service to assist his wife in the "bearing down" process.

The stated purpose of the book, "to serve as an inspiration and guide," may cue the physician to the interests and aspirations of an important segment of the childbearing population. These couples plan, prepare for and want an active role in childbirth. They want to be treated individually, intelligently and respectfully.

Karen Michele is a professional photographer who specializes in children's photography. Perhaps that explains why the photos are so forthright. They capture the drama of the moment with considerable brightness and gloss. One cannot help but wonder whether so much light was jarring to her subjects.

One also wonders whether a new mother-to-be might find the photos a bit insensitive and frightening. Although the outcomes are sublime, there are tortured moments caught in still photos that may concern those who neglect to read the text or who do not understand the process.

There is also a sense of staging, of spotlighting, that conflicts with the sense of privacy and intimacy that one associates with childbirth.

The technical explanations offered by

Elisabeth Bing, the well-known and authoritative childbirth educator and author, are excellent. They add understanding and dimension to the photographs. Her descriptions of the procedures are made very clear for lay persons, but an index would have made this volume a more useful reference.

Perhaps the objective of the book, to document the work, joy and emotions of childbirth, was too ambitious. As the book attempts to illustrate, the experience is somewhat different for everyone. It is probably impossible to get a perfect picture of such a multidimensional event. However, the authors deserve full credit for trying.

DAVID A. KLIOT, MD
Brookdale Hospital Medical Center
New York City 11212

DRUGS USED WITH NEONATES AND DURING PREGNANCY

Second Edition. By Ina Lee Stile, PharmD, Thomas Hegyi, MD, and I. Mark Hiatt, MD. 154 pp. Oradell, NJ, Medical Economics Books, 1984. $10.95 (softcover).

This small handbook is an attempt to catalog all the current pharmacologic agents used in the perinatal period. The authors (a clinical pharmacologist and two neonatologists) draw their experiences from two regional perinatal centers that service an urban and a suburban community.

The sections of the book lead systematically from pregnancy to the newborn. Drugs that are used in pregnancy and can appear in breast milk are highlighted, followed by an attempt to classify drug use by system (cardiovascular, respiratory, endocrine). Finally, some miscellaneous topics are included (drug withdrawal, nutritional requirements).

Several overall comments are in order. First, the title is awkward. Most perinatal specialists think of the biological maternal-infant unit in chronologic terms, first pregnancy and then the fetus and newborn. That is how the table of contents reads and that is what the title should reflect. Second, other than the publisher's note, there is little narrative, except for a brief discussion of neonatal pharmacology and drug withdrawal. A short introduction to each section would have provided a framework for the tabular approach of the drugs listed. Thirdly, there are very specific problems with the multiple listing of drugs.

The section on drugs in pregnancy deals only with medications that have adverse effects on the fetus or newborn. No attempt is made to list drugs that are therapeutic in pregnancy. For example, no tocolytic agents to avert premature labor are mentioned. Dexamethasone (used in many prenatal centers) usage in premature labor—with fetuses of 30-32 weeks—to stimulate surfactant production is not listed.

For the most part, little insight is given into deciding which drugs to use for specific disorders. There are exceptions; for example, the discussion of anti-convulsive therapy is more discriminating in the choice of drug usage.

Certain omissions could have been avoided. For instance, glucose and dextrose/water in various concentrations are not mentioned as therapeutic agents.

The index is somewhat misleading. Though it includes many pathologic entries, they refer more often than not to adverse effects or complications rather than to therapeutic approaches. For example, hypoglycemia is cited on nine pages, but only once is an approach to the treatment of neonatal hypoglycemia cited—glucagon is suggested on p 86, but there is no mention of glucose treatment. Common problems such as hypocalcemia are not even listed in the index.

In short, this manual may not be very helpful to the providers of care to neonates, but certain sections, such as neonatal nutritional requirements and drug therapy during pregnancy, may be beneficial as reference material.

ANGELO FERRARA, MD
New York University Medical Center
New York City 10016

IS IT WORTH DYING FOR?

By Robert S. Eliot, MD and Dennis L. Breo. 248 pp. New York, Bantam Books, 1984. $14.95 (hardcover)

This is a lay-oriented book that presents the argument for emotional stress as a central risk factor for cardiovascular disease, and makes general recommendations for managing emotional stress and for modifying other major risk factors. Eliot is highly qualified to present this argument given the importance of his recent research on physiological reactivity to psychological stress situations and his personal experience with stress management following his own heart attack. Breo brings to the technical content of the book a straightforward, uncomplicated, and easily comprehended style that makes the book accessible to a varied audience. The sections on stress management and on altering risk factor behaviors reflect the input of Eliot's multidisciplinary team at the University of Nebraska.

The book is organized under two general headings: Stress and the Hot Reactor and Learning to Manage Stress. The first section presents essential information about the cardiovascular system and about two stress responses—short term alarm and long term vigilance—with emphasis on Eliot's concept of physiological "hot reactors." Three subtypes of hot reactors are characterized physiologically and by case examples, and they are related to major cardiovascular disorders. The section concludes with self-assessment questionnaires to index stress levels, and with instructions for self-assessment of hot reactivity by conducting mental stress tests of the sort used at Eliot's Life Stress Simulation Laboratory. The second section includes chapters on stress management including changing stress-producing thought patterns, using relaxation exercises, using leisure time and social supports, and changing job stress, as well as chapters on modification of other risk factors including physical fitness, dietary changes, smoking cessation and moderation of alcohol and caffeine intake. The chapters are all relatively short, with liberal subheadings, making reading and reference use easy.

The most unique contribution of this book is its presentation for the layman of Eliot's work on physiological reactivity to psychological challenge situations. The sections that present these concepts are clearly written and accessible to the nonphysician audience. Distinctions are made between the hot reactor concept and the better known Type A behavior pattern.

The chapters on the sources of stress and on stress management sometimes suffer from an unfortunate simplistic psychological idealism that is a common pitfall of stress management writing. As written, the book implies that the steps required to manage stress are straightforward and easy to accomplish. If it were really so easy, and if people were really so logical, then there wouldn't be so much of a problem! In fact, the problems of emotional stress management are more complex that this book implies, and the issues involved deserve a more thoughtful and critical discussion. To their credit, the authors probably realize this, but have simply chosen to write a different kind of book. In spite of these concerns, the stress management sections are fundamentally sound and emphasize several important underlying principles: the role of unrealistic personal expectations in producing stress, the importance of flexibility and of assuming responsibility for one's reactions, and the realistic role of relaxation exercises in the panoply of stress management techniques.

The chapters on exercise, diet, and moderation of alcohol and caffeine are straightforward presentations of basic recommendations in these areas, with appropriate referrals to community resources. In spite of a generally balanced discussion of exercise and fitness, some experts would find the recommended exercises for cardiovascular conditioning (20 minutes of brisk walking, three to five times per week) to be insufficient to produce a significant cardiovascular conditioning effect.

The book achieves its primary purpose of emphasizing that stress is an important factor in the etiology and progress of heart disease, and providing an overview of the measures one can take to moderate stress and reduce other risk factors. The book is worth reading for anyone concerned with preventing heart disease or with recovery from a major cardiovascular disorder.

MERRILL P. ANDERSON, PHD
Houston Cardiovascular
Rehabilitation Center
Houston, TX 77030

CONGENITAL HEART DISEASE AFTER SURGERY: BENEFITS, RESIDUA, SEQUELAE

Edited by Mary Allen Engle, MD and Joseph K. Perloff, MD. 420 pp, illustrated. New York, Yorke Medical Books, 1983. $40.00 (hardcover)

This publication, aptly dedicated to Dr Helen Taussig, is a remarkable compendium of up-to-date experiences and results in pediatric cardiology. During the last 40 years, physicians in this subspecialty of pediatrics have succeeded in treating, partially or completely, most of the cardiac patients in the United States after the first few years of life. The focus of action has shifted to the newborn and toddler, and the remarkable success achieved is truly "Made in the USA." From the start some of our best pediatricians have proceeded to develop one technique after another in a steady outpouring of novel ways to deal with the challenge of diagnosing and treating complicated circulatory abnormalities.

This symposium provides an extensive look at what has been done in a relatively short period of time; it presents current techniques and offers a glimpse into the future as perceived by some of the keenest and best-informed physicians. Indeed, Perloff and Engle have carefully canvassed 35 experts, and each one has given a detailed account of present day knowledge in the field of pediatric cardiology.

The editors have divided the material into six parts, starting with an interesting outlook on congenital heart disease and its origins. The chapters on non-cyanotic and cyanotic malformations contain a discussion about the most significant clinical situations that face pediatricians, and does so commendably in barely over 150 pages.

Part IV deals with postoperative function. There is a wealth of information here that should be carefully considered by pediatricians caring for children with cardiac problems, and also by colleagues who inherit these patients when they are adults. This is a difficult transition for such patients due to the lack of experience in this field by internists and adult cardiologists, and it is hoped that greater communication between pediatric and adult cardiologists will be achieved.

Part V offers useful and timely information on employment, insurability and the effects of pregnancy on young cardiac patients.

Finally, in Part VI the reader is presented with a broad personal view of the field by Edward, Nadas, and Kirklin. Their enormous contribution to the speciality in the areas of pathology, cardiology, and surgery gives their final remarks the sharpness and weight that enriches the content of this book. As a pediatric cardiologist, I found this symposium to be well organized, timely, and compelling. But this publication should be even more essential to physicians who must deal with the long-term care of young cardiac patients with heart problems.

FILIPPO A. BALBONI, MD
St Francis Hospital
Roslyn, NY 11576

CLINICAL CARDIOVASCULAR AND PULMONARY PHYSIOLOGY

By Clive Rosendorff, MD, PhD. 382 pp. New York, Raven Press, 1983. $17.50 (softcover)

As stated in the preface, the major theme of this book is to promote an understanding of the clinical phenomena associated with cardiovascular and pulmonary physiology. Such an understanding appears to be an appropriate and useful addition to the medical literature.

Brevity has often been promoted at the expense of adequate explanation. In many areas the author, a physician and professor of physiology, describes a phenomenon with little explanation of its mechanisms. For example, in the section on the electrocardiogram, various types of cardiac arrhythmias are described in detail, but the bases of cardiac arrhythmias—the reentry mechanism, for one—are not explained. Such explanations could have been useful for an understanding of the mechanism of action of anti-arrhythmic drugs.

The book is divided into two parts. In the section on the cardiovascular system, the emphasis is on linking knowledge of the physiology to an understanding of clinical diseases. The discussions include clinical complications of circulatory shock and treatment of heart failure. In contrast, little effort has been made to correlate pulmonary physiology to disease states. Only 12 pages have been devoted to a discussion of clinical applications of pulmonary physiology, and the most common of all pulmonary diseases, pneumonia, is not discussed.

The author fails to utilize the advantage of integrating the physiology of both systems to explain disease states. For example, chronic obstructive lung disease could have been discussed utilizing both cardiovascular and pulmonary physiology.

Finally, there is one glaring error in the section on treatment of heart failure. Diuretics are classified into three types: thiazide diuretics, potassium sparing diuretics including amiloride and ethacrynic acid, and aldosterone antagonists. Ethacrynic acid is not a potassium sparing diuretic but a loop diuretic, and aldosterone antagonists are a type of potassium sparing diuretic.

MAN SEOK OH, MD
State University of New York
Downstate Medical Center
New York, NY 11203

ROCHE VERSUS ADAMS

By Stanley Adams. 236 pp. London, Jonathan Cape, 1984. £8.95

In February 1973, Stanley Adams told the European Economic Commission (EEC) about illicit trading practices of the multinational pharmaceutical company Hoffman-La Roche. Adams had worked for the Swiss-based company for nine years and had recently been promoted to World Product Manager.

Although he enjoyed the luxurious lifestyle that goes with a major executive position, some of the practices of the company alarmed him, especially a policy of price fixing and market sharing with competitors, and control of the worldwide vitamin market.

Adams had an opportunity to curb such practices when Switzerland signed a free trade agreement with the EEC. The EEC used the information Adams provided in an investigation of Roche, and three years later they fined the company £240,000 (approximately $300,000)—less than 1% of their total annual turnover but a fine that stung the company nonetheless—for breaking EEC laws on free competition.

For Stanley Adams, however, blowing the whistle on Hoffman-La Roche led to a nightmare. Adams left Roche and planned to start a pig farm in Italy. In December 1974 he and his family were crossing the border from Italy into Switzerland, when he was arrested. Given no reason for his arrest, Adams was put into solitary confinement in a Swiss jail. Roche had lodged a complaint that led to Adams' detention.

In the appalling days that followed, his wife tried unsuccessfully to contact her husband. She was interrogated by Swiss authorities and told that, if convicted, Stanley Adams faced up to 20 years in jail. But what was the charge? Adams believed that he was doing his duty to consumers of Roche products by exposing the firm's practices. In Switzerland, however, big business is legally considered a matter of national security, so Marilene Adams was told that her husband faced charges of industrial espionage and treason. To this day no one knows what pressure she was put under by the Swiss authorities. All that is known is that Marilene Adams committed suicide.

Lying in prison bewildered and dazed, Adams was not informed of his wife's suicide until two days later. He was then denied the right to attend her funeral. When at last released on bail almost three months later, Stanley Adams' nightmare continued. The bank funds, previously arranged for his new business in Italy, were not forthcoming. Adams was unpopular as a result of interviews he had given that told of under the table transactions between Italian politicians and Roche concerning the Roche-owned chemical factory in Seveso, which exploded in 1976 venting a cloud of dioxin over the city.

Given a three-year suspended sentence in Switzerland, Adams won the unanimous backing of the European Parliament for his actions, (the first unanimous vote in the Parliament's history) but faced bankruptcy nonetheless. Adams counted on receiving £500,000. The EEC paid him a paltry £20,000 (approximately $25,000) for his pains; it was the EEC who had betrayed Adams by disclosing that he had told them about Roche's practices.

Stanley Adams has described his experiences in the book *Roche versus Adams*. The book is a horrific story about the power of a large company to take action that can ruin a man's life, how an important country like Switzerland defends the illicit trading practices of its companies, and the bungling of the European Economic Commission.

Adams worked for Roche for five years in Latin America, and has traveled throughout developing countries. He details the business practices of Roche that led him to report to the EEC—of how Roche eliminated fair competition and of the prices the company was able to charge. d-Biotin, for example, which cost $0.56 a gram to produce, was sold at $10 a gram, almost 20 times as much. The book provides insights into the way Hoffman-La Roche operates in the developing world. "When news came of an influenza epidemic, for instance, in India," says Adams, "instead of putting vitamin C out in greater quantities, we [Roche] would control the quantities going out and usually increase the price."

Government economists in Colombia were puzzled as to why pharmaceutical companies were keen to expand, when the companies *appeared* to be making only 6% profit on their activities. An investigation revealed that foreign-owned multinationals were overcharging their Colombian subsidiaries for ingredients by 155%. Librium, which is made by Roche, was "overpriced by a staggering 6,478%," says Adams. Had the multinationals been charging their subsidiaries an appropriate price, then the Colombian companies would have been making 79% profit, not 6%. Colombia was cheated out of taxes on profits. "In moral terms," Adams writes, "this amounts to exploitation." Whereas the companies appeared to be making little money in Colombia, they were making it elsewhere—in Montevideo, Uruguay, for example; profits made there are not taxed.

Adams now lives in Britain, where he continues his struggle for justice against the organizations that have wronged him—"not only for me," he says, "but for other potential whistle blowers who think 'its not worth it' and keep silent. We need them. The fiercer the pressures to keep silent, the more urgent the need is for people to speak out."

JOHN MADELEY

Mr. Madeley is a British journalist who contributes regularly to the Journal.

BOOKS RECEIVED

CARDIOLOGY

Cardiology 1984. By William C. Roberts, MD, et al. 512 pp, illustrated. New York, Yorke Medical Books, 1984. $49.50 (hardcover)

Classics of Cardiology. Volume III. By John A. Callahan, MD, Thomas E. Keys, MA, Jack D. Key, MA. 646 pp, illustrated. Florida, Robert E. Krieger Publishing Co, 1983. $36.40 (hardcover)

Tachycardias: Mechanisms, Diagnosis, Treatment. By Mark E. Josephson, MD, Hein J. J. Wellens, MD. 553 pp, illustrated. Pennsylvania, Lea & Febiger, 1984. $57.50 (hardcover)

GENETICS

The Fragile X Syndrome. Diagnosis, Biochemistry and Intervention. Edited by Randi Jenssen Hagerman, MD, Pamela McKenzie McBogg, MD. 239 pp, illustrated. Colorado, Spectra Publishing Co, 1983. $16.95 (softcover)

HEALTH CARE

Prison Health Care. Edited by Richard Smith BSc MB ChB. 182 pp, illustrated. England, The Devonshire Press, 1984. (paperback)

HISTORY OF MEDICINE

Conversations in Medicine. The story of Twentieth-Century American Medicine in the Words of Those Who Created It. By Allen B. Weisse, MD. 443 pp. New York, New York University Press, 1984. $25.00 (clothcover)

INTERNAL MEDICINE

Antinuclear Antibodies. Contemporary Techniques and Clinical Application to Connective Tissue Diseases. By Gale A. McCarty, Donald W. Valencia, Marvin J. Fritzler. 95 pp, illustrated. New York, Oxford University Press, 1984. $29.95 (hardcover)

On Diagnosis: A Systemic Approach. By Michael L. Glenn, MD. 220 pp, illustrated. New York, Brunner/Mazel, Publishers, 1984. $20.00 (hardcover)

Update V. Harrison's Principles of Internal Medicine. Edited by Robert G. Petersdor, MD, Raymond D. Adams, MD, Eugene Braunwald, MD, Kurt J. Isselbacher, MD, Joseph B. Martin, MD, Jean D. Wilson, MD. 306 pp, illustrated. McGraw-Hill Book Company, New York, 1984. $35.00 (hardcover)

INTERNATIONAL MEDICINE

Health Problems of Yemen and Its Population. By M. C. Thuriaux. 145 pp, tables. Florida, Field Research Projects, 1983. $12.50 (hardcover)

MEDICAL EDUCATION

How to Survive Medical School. By Toni Martin, MD. 180 pp. New York, Penguin Books, 1983. $5.95 (paperback)

MISCELLANEOUS

Diet & Cancer. There is a connection. By Kristin White. 256 pp. New York, Bantam Books, 1984. $3.95 (paperback)

Dietwalk. The Doctor's Fast & Easy 3-Day Superdiet. By Fred A. Stutman, MD. 184 pp, illustrated. Pennsylvania Medical Manor Books, 1984. $8.95 (paperback)

Heading Toward Omega. In Search of the Meaning of Near-Death Experience. By Kenneth Ring, PhD, 348 pp. New York, William Morrow and Company, 1984. $15.95 (softcover)

Mind Over Back Pain: A radically new approach to the diagnosis and treatment of back pain. By John Sarno, MD. 124 pp, illustrated. New York, William Morrow and Company, 1984. $12.95 (hardcover)

The Road Back to Health: Coping With the Emotional Side of Cancer. By Neil A. Fiore, PhD. 256 pp. New York, Bantam Books, 1984. $6.95 (paperback)

Understand Your Backache. A Guide to Prevention, Treatment, and Relief. By Rene Gailliet, MD. 200 pp, illustrated. Pennsylvania, F. A. Davis Company, 1984. $10.95 (softcover)

OBSTETRICS AND GYNECOLOGY

Preterm Birth: Causes, Prevention and Management. Edited by Fritz Fuchs, MD, Phillip G. Stubblefield, MD. 392 pp, illustrated. New York, Macmillan Publishing Company, 1984. $48.00 (hardcover)

OPHTHALMOLOGY

Contact Lens Primer—A Manual. By Barry A. Weissman, OD, PhD. 138 pp, illustrated. Pennsylvania, Lea & Febiger, 1984. $12.50 (paperback)

PEDIATRICS

Cancer Therapy in Children. Edited by Carl Pochedly, MD. 233 pp, illustrated. New Jersey, Slack, Inc, 1983. $27.50 (hardcover)

Color Atlas of The Newborn. By R. D. G. Milner, MD, S. M. Herber, MB. 136 pp, illustrated. New Jersey, Medical Economics Company, 1984. $44.95 (hardcover)

Pediatric Risk Factors for Major Chronic Disease. By Christine L. Williams, MD, MPH. 159 pp, illustrated. Missouri, Warren H. Green, Inc, 1984 $22.50 (hardcover)

PSYCHIATRY

Differential Therapeutics in Psychiatry: The Art and Science of Treatment Selection. By Allen Frances, MD, John Clarkin, PhD, Samuel Perry, MD. 420 pp. New York, Brunner/Mazel Publishers, 1984. $30.00. (hardcover)

RADIOLOGY

Christensen's Introduction to The Physics of Diagnostic Radiology. Third Edition. By Thomas S. Curry III, MD, James E. Dowdey, PhD, Robert C. Murry, Jr, PhD. 515 pp, illustrated. Pennsylvania, Lea & Febiger, 1984. $30.00 (hardcover)

Invasive Uroradiology. A Manual of Diagnostic and Therapeutic Techniques. By Morteza K. Elyaderani, MD, Stanley J. Kandzari, MD, Wilfrido R. Castaneda, MD, Paul H. Lange, MD. 250 pp, illustrated. Massachusetts, The Collamore Press, 1984. $40.00 (hardcover)

SPORTS MEDICINE

Principles of Sports Medicine. Edited by W. Norman Scott, MD, Barton Nisonson, MD, James A. Nicholas, MD. 433 pp, illustrated. Maryland, Williams & Wilkens, 1984. $65.00 (hardcover)

CORRECTION

In the review of *Malignant Lymphomas* (1984; 84:270–271), the name of the coauthor, P.P. Rosen, MD, was omitted.

In addition to these listings, the Journal *will publish obituaries written by physician readers. Inquiries should first be made to the Editor.*

Marion William Astarita, MD, San Diego, California. Died April 6, 1981; age 91. Dr Astarita was a 1920 graduate of the State University of New York Downstate Medical Center and was a member of the New York County Medical Society and the Medical Society of the State of New York.

Morris M. Banowitch, MD, Hallandale, Florida. Died April 19, 1984; age 93. Dr Banowitch was a 1914 alumnus of the State University of New York Downstate Medical Center. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Else Anna S. Barthel, MD, Bronxville. Died September 10, 1983; age 91. She was a 1920 alumna of Cornell University Medical College. Dr Barthel was a Diplomate of the American Board of Dermatology, Inc. Her memberships included the Academy of Medicine, the American Academy of Dermatology, the New York County Medical Society and the Medical Society of the State of New York.

Wilford Wendell Berge, MD, Pittsford. Died June 12, 1984; age 70. He was a 1941 graduate of Northwestern University Medical School. Dr Berge was a Fellow of the American College of Surgeons and a Diplomate of the American Board of Surgery. He was a member of the Academy of Medicine, the New York State Surgical Society, the Medical Society of the County of Monroe and the Medical Society of the State of New York.

David Birnbaum, MD, Asheville, North Carolina. Died September 10, 1983; age 79. He was a 1931 graduate of New York University College of Medicine. Dr Birnbaum was a member of the New York County Medical Society and the Medical Society of the State of New York.

Herbert Blau, MD, New York. Died March 8, 1984; age 82. Dr Blau was a 1926 graduate of Columbia University College of Physicians and Surgeons. He was a member of the New York County Medical Society and the Medical Society of the State of New York.

Raymond Joseph Bowen, MD, Contoucook, New Hampshire. Died May 30, 1984; age 86. Dr Bowen was a 1924 alumnus of Columbia University College of Physicians and Surgeons. He was a member of the Broome County Medical Society and the Medical Society of the State of New York.

Christy F. Castiglia, MD, Tonawanda. Died May 25, 1984; age 74. Dr Castiglia was a 1934 graduate of the University of Buffalo School of Medicine and was a member of the Academy of Medicine, the Medical Society of the County of Erie and the Medical Society of the State of New York.

Edward Henry Chappelle, MD, Rochester. Died May 26, 1984; age 59. He was a 1957 alumnus of Howard University College of Medicine. Dr Chappelle was a member of the New York State Society of Internal Medicine, the Academy of Medicine, the Medical Society of the County of Monroe and the Medical Society of the State of New York.

Nathan W. Chaikin, MD, New York. Died May 17, 1984; age 87. He was a 1927 graduate of the University of Buffalo School of Medicine. Dr Chaikin was a Fellow of the American College of Gastroenterology and the American College of Physicians, and a Diplomate of the American Board of Internal Medicine. His memberships included the New York Gastroenterological Society, the International Society of Internal Medicine, the Pan American Medical Association, the American Geriatrics Society, the New York County Medical Society and the Medical Society of the State of New York.

Lester Clahr, MD, New York. Died April 30, 1984; age 78. Dr Clahr was a 1932 graduate of the State University of New York Downstate Medical Center. He was a member of the New York County Medical Society and the Medical Society of the State of New York.

Theodore David Cohn, MD, Brooklyn. Died June 1, 1984; age 76. He was a 1931 alumnus of the State University of New York Downstate Medical Center. Dr Cohn was a Fellow of the American College of Physicians and a Diplomate of the American Board of Internal Medicine. His memberships included the Academy of Medicine, the New York Cardiological Society, the Clinical Society of the New York Diabetes Association, the American Geriatrics Society, the American Society of Hematology, the Medical Society of the County of Kings and the Medical Society of the State of New York.

Nicholas Joseph Colao, MD, Peekskill. Died June 9, 1984; age 76. Dr Colao was a 1936 graduate of Georgetown University School of Medicine. He was a member of the Academy of Medicine, the American School Health Association, the Medical Society of the County of Westchester and the Medical Society of the State of New York.

John Totterdale Cole, MD, Jericho. Died July 24, 1984; age 70. He was a 1940 graduate of the University of Maryland School of Medicine. Dr Cole was a Fellow of the American College of Obstetricians and Gynecologists and a member of the New York County Medical Society and the Medical Society of the State of New York.

Josue M. Corcos, MD, New York. Died May 29, 1984; age 55. Dr Corcos was a 1955 alumnus of the Université de Paris

Faculté de Médecine. He was a member of the American Rheumatism Association, the New York County Medical Society and the Medical Society of the State of New York.

John Melton Cotton, MD, New York. Died June 7, 1984; age 76. He was a 1932 graduate of Tulane University School of Medicine. Dr Cotton was a Diplomate of the American Board of Psychiatry and Neurology. His memberships included the Academy of Medicine, the American Psychiatric Association, the Society for Experimental Biology and Medicine, the Association for Research in Nervous and Mental Disease, the New York County Medical Society and the Medical Society of the State of New York.

Arthur Michael Epstein, MD, Glen Cove. Died June 26, 1984; age 42. He was a 1968 graduate of the University of Pittsburgh School of Medicine. Dr Epstein was a Diplomate of the American Board of Ophthalmology and a member of the American Academy of Ophthalmology and Otolaryngology, the Nassau County Medical Society and the Medical Society of the State of New York.

Caspar Folkoff, MD, New York. Died May 15, 1984; age 91. Dr Folkoff was a 1923 graduate of Johns Hopkins University School of Medicine. He was a Diplomate of the American Board of Internal Medicine and a member of the Academy of Medicine, the New York County Medical Society and the Medical Society of the State of New York.

Walter Freund, MD, Oswego. Died June 9, 1984; age 73. Dr Freund was a 1937 graduate of the Universität Zurich Medizinische Fakultät, Zurich. He was a member of the Academy of Medicine, the Medical Society of the County of Oswego and the Medical Society of the State of New York.

John G. Grozine, MD, White Plains. Died May 15, 1984; age 78. Dr Grozine was a 1940 graduate of the Università di Napoli di Medicina e Chirurgia, Napoli. He was a member of the Academy of Medicine, the New York County Medical Society and the Medical Society of the State of New York.

Joseph P. Harrington, MD, Babylon. Died February 12, 1984; age 58. Dr Harrington was a 1958 alumnus of New York Medical College, Flower and Fifth Avenue Hospitals. He was a member of the Suffolk County Medical Society and the Medical Society of the State of New York.

Reid Russell Heffner, MD, Buffalo. Died July 1, 1984; age 80. He was a 1931 alumnus of Johns Hopkins University School of Medicine. Dr Heffner was a Fellow of the American College of Physicians and a Diplomate of the American Board of Internal Medicine. His memberships included the New York Gastroenterological Society, the American Gastro-enterological Association, the Medical Society of the County of Westchester and the Medical Society of the State of New York.

George Aloysius Howley, MD, Pelham Manor. Died June 29, 1984; age 80. He was a 1929 alumnus of Georgetown University School of Medicine. Dr Howley was a Fellow of the American College of Surgeons and a member of the Bronx County Medical Society and the Medical Society of the State of New York.

Gunther M. Jacob, MD, Tappan. Died February 2, 1984; age 68. He was a 1943 alumnus of the Universität Zurich Medizinische Fakultät, Zurich. Dr Jacob was a Fellow of the American Psychiatric Association and a Diplomate of the American Board of Psychiatry and Neurology. He was a member of the New York County Medical Society and the Medical Society of the State of New York.

Morris Jaffe, MD, New York. Died June 12, 1984; age 93. He was a 1917 alumnus of the State University of New York Downstate Medical Center. Dr Jaffe was a Fellow of the American College of Surgeons and a Diplomate of the American Board of Ophthalmology. He was a member of the American Academy of Ophthalmology and Otolaryngology, the New York County Medical Society and the Medical Society of the State of New York.

Jacques B. Jakoff, MD, Miami Beach, Florida. Died April 20, 1983; age 76. Dr Jakoff was a 1933 alumnus of the University of Sofia Faculty of Medicine, Sofia. He was a member of the American Academy of Family Physicians, the New York County Medical Society and the Medical Society of the State of New York.

S. Seymour Joseph, MD, Shoreview, Minnesota. Died March 5, 1984; age 68. He was a 1941 alumnus of the Università degli Studi di Bologna, Facoltà di Medicina e Chirurgia, Bologna. Dr Joseph was a Diplomate of the American Board of Psychiatry and Neurology and a member of the American Psychiatric Association, the Medical Society of the County of Westchester and the Medical Society of the State of New York.

Austin L. Joyner, MD, Hamden, Connecticut. Died May 18, 1984; age 82. Dr Joyner was a 1934 alumnus of Duke University School of Medicine. He was a member of the Medical Society of the County of Rockland and the Medical Society of the State of New York.

Max Kimbrig, MD, Boca Raton, Florida. Died April 27, 1984; age 87. He was a 1920 alumnus of New York University College of Medicine. Dr Kimbrig was a member of the Suffolk County Medical Society and the Medical Society of the State of New York.

Stephen Lantos, MD, Forest Hills. Died June 21, 1984; age 76. He was a 1933 graduate of the Medizinische Fakultät der Universität, Vienna. Dr Lantos was a member of the American Thoracic Society, the Medical Society of the County of Queens and the Medical Society of the State of New York.

Frederick Lehmann, MD, New York. Died April 25, 1984; age 88. He was a 1921 graduate of Johann-Wolfgang-Goethe-Universität Medizinische Fakultät, Frankfurt-Am-Main, Prussia. Dr Lehmann was a Diplomate of the American Board of Otolaryngology, and was a member of the New York County Medical Society and the Medical Society of the State of New York.

James Alan Leiter, MD, New City. Died June 11, 1984; age 43. He was a 1967 alumnus of New York University College of Medicine. Dr Leiter was a Fellow of the American College of Surgeons and a Diplomate of the American Board of Urology. He was a member of the Medical Society of the County of Rockland and the Medical Society of the State of New York.

John James Mead III, MD, New York. Died May 14, 1984; age 60. He was a 1947 graduate of Georgetown University School of Medicine. Dr Mead was a Fellow of the American College of Physicians, the American College of Cardiology, the American College of Chest Physicians, the American College of Angiology and the American College of Preventive Medicine and a Diplomate of the American Board of Internal Medicine. His memberships included the New York Cardiological Society, the American Geriatrics Society, the International Society of Internal Medicine, the Pan American Medical Association, the New York County Medical Society and the Medical Society of the State of New York.

Carl George Merkel, MD, Saranac Lake. Died June 11, 1984; age 75. He was a 1933 graduate of Johns Hopkins University School of Medicine. Dr Merkel was a Fellow of the American College of Surgeons and the American College of Chest Physicians, and a Diplomate of the American Board of Thoracic Surgery. His memberships included the American Association for Thoracic Surgery, the American Thoracic Society, the Medical Society of the County of Franklin and the Medical Society of the State of New York.

Frank Meyers, MD, Buffalo. Died May 28, 1984; age 78. He was a 1929 graduate of the University of Buffalo School of Medicine. Dr Meyers was a Fellow of the American College of Physicians and a Diplomate of the American Board of Internal Medicine. He was a member of the Medical Society of the County of Erie and the Medical Society of the State of New York.

Oscar J. Mink, MD, Hastings on Hudson. Died June 12, 1984; age 84. Dr Mink was a 1924 graduate of Georgetown University School of Medicine. He was a member of the Academy of Medicine, the Medical Society of the County of Westchester and the Medical Society of the State of New York.

Walter Niemann, MD, Birmingham, Alabama. Died June 8, 1984; age 93. Dr Niemann was a 1917 alumnus of Kaiser-Wilhelms-Universität Medizinische Fakultät, Strassburg. He was a member of the Nassau County Medical Society and the Medical Society of the State of New York.

Frederick J. Pollack, MD, Elmhurst. Died May 7, 1984; age 96. He was a 1914 graduate of Rheinische Friedrich-Wilhelms-Universität Medizinische Fakultät, Bonn, Prussia. Dr Pollack was a member of the American Geriatrics Society, the Medical Society of the County of Queens and the Medical Society of the State of New York.

Daniel Rakov, MD, Maybrook. Died May 50, 1984; age 84. Dr Rakov was a 1922 graduate of the State University of New York Upstate Medical Center. He was a member of the Medical Society of the County of Orange and the Medical Society of the State of New York.

Keeve Rosenthal, MD, Bronx. Died May 18, 1984; age 77. He was a 1931 alumnus of New York University College of Medicine. Dr Rosenthal was a member of the American Academy of Family Physicians, the Bronx County Medical Society and the Medical Society of the State of New York.

Abraham S. Rothberg, MD, New York. Died May 4, 1984; age 84. He was a 1926 alumnus of the University of Maryland School of Medicine. Dr Rothberg was a Fellow of the American College of Surgeons and a Diplomate of the American Board of Orthopedic Surgery. He was a member of the American Academy of Orthopaedic Surgeons, the American Geriatrics Society, the New York County Medical Society and the Medical Society of the State of New York.

Samuel D. Shapiro, MD, Hollywood, Florida. Died May 23, 1984; age 84. Dr Shapiro was a 1924 alumnus of New York Medical College, Flower and Fifth Avenue Hospitals. He was a member of the Bronx County Medical Society and the Medical Society of the State of New York.

Raymond Edward Slevin, MD, Miller Place. Died July 7, 1984; age 45. He was a 1966 graduate of the New Jersey College of Medicine and Dentistry. Dr Slevin was a member of the Suffolk County Medical Society and the Medical Society of the State of New York.

Julius Steckler, MD, Brooklyn. Died May 25, 1984; age 72. He was a 1936 alumnus of the Université de Lausanne Faculté de Médecine. Dr Steckler was a member of the New York County Medical Society and the Medical Society of the State of New York.

Felix Taubman, MD, Brooklyn. Died June 18, 1984; age 68. He was a 1942 graduate of Marquette University School of Medicine. Dr Taubman was a Fellow of the American College of Chest Physicians, the American College of Cardiology and the American College of Physicians, and a Diplomate of the American Board of Internal Medicine. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Raeburn J. Wharton, MD, Johnson City. Died July 15, 1984; age 92. Dr Wharton was a 1916 alumnus of Albany Medical College of Union University. He was a Fellow of the American College of Physicians and a member of the Academy of Medicine, the American Academy of Pediatrics, the Broome County Medical Society and the Medical Society of the State of New York.

Thomas Scudder Winslow, MD, New York. Died April 2, 1984; age 68. He was a 1942 graduate of Cornell University Medical College. Dr Winslow was a Fellow of the American College of Surgeons and a Diplomate of the American Board of Surgery. His memberships included the Academy of Medicine, the New York State Surgical Society, the New York County Medical Society and the Medical Society of the State of New York.

Abraham S. Wilner, MD, Palm Springs, California. Died November 1, 1983; age 81. Dr Wilner was a 1931 alumnus of Laval University Faculty of Medicine, Quebec. He was a member of the New York County Medical Society and the Medical Society of the State of New York.

John S. Witkowski, MD, Niagara Falls. Died April 30, 1984; age 79. Dr Witkowski was a 1931 graduate of Stritch School of Medicine of Loyola University. He was a member of the American Academy of Family Physicians, the Medical Society of the County of Niagara and the Medical Society of the State of New York.

Eugene F. Wolff, MD, Newburgh. Died April 14, 1984; age 81. Dr Wolff was a 1931 alumnus of Universität Koln-Cologne-Medizinische Fakultät, Koln, Prussia. His memberships included the New York State Society of Internal Medicine, the American Geriatrics Society, the Medical Society of the County of Orange and the Medical Society of the State of New York.

Otto Zelezny, MD, Bronx. Died April 15, 1984; age 84. Dr Zelezny was a 1925 graduate of Medizinische Fakultät der Universität, Vienna. He was a member of the American Geriatrics Society, the Bronx County Medical Society and the Medical Society of the State of New York.

Guidelines for authors

ORIGINALITY

The *New York State Journal of Medicine* welcomes research papers and original essays on the practice of medicine, medical education, public health, the history of medicine, medicolegal matters, legislation, ethics, the mass media and socioeconomic issues in health care.

Manuscripts should be prepared according to the "Uniform requirements for manuscripts submitted to biomedical journals" (*NY State J Med* 1983; 83:1089–1094). The requirements were established by the International Committee of Medical Journal Editors, of which the *Journal* is a participating member. These Guidelines are intended to highlight aspects of the *Journal*'s particular style of publication.

A manuscript will be considered for publication if it is original, has not been published previously in whole or in part in either a medical journal or a lay publication, and is not simultaneously under consideration elsewhere. A copy of any possibly duplicative material, such as a reference "in press," should be submitted along with the manuscript.

PREPARATION

An original typewritten or "word-processed" manuscript and two photocopies (to facilitate outside review) are required. If the manuscript is not accepted for publication, the original and one copy will be returned. All figures must be submitted in triplicate. The manuscript should be double-spaced throughout, including references, tables, legends, quotations, and acknowledgments. A separate title page should include the full title of the paper in upper and lower case type, the names of the authors exactly as they should appear in print (including their highest academic degree), an abbreviated title of no greater than 40 spaces for use as a running foot, and the names of all providers of funding for research on which the paper is based. Information on the amount and allocation of funding is optional.

A corresponding author should be designated in the covering letter. Authors should list their title and affiliation at the time they did the work, and, if different, their present affiliation. The addresses and telephone numbers of all authors should be supplied for editorial purposes. All authors of a manuscript are responsible for having read and approved it for submission.

CATEGORIES

Research Papers should be limited to 2,500 words and should include the following sections: Introduction, Methods, Results, Discussion, and References. Multiple subheadings and numbered lists are discouraged. An abstract limited to 150 words should state the reasons for the study, the main findings, and their implications. Statistical evaluations should be described in the Methods section, and the name and affiliation of the statistician should be included in the acknowledgments if this individual is not listed as a coauthor. Reports of experiments involving human subjects must include a description in the Methods section of the informed consent obtained and a statement that the procedures followed were approved by an institutional research review committee. Anonymity of patients must be preserved. Reports of experiments on animals must note which guidelines were followed for the care and use of laboratory animals.

Case Reports should be limited to 1,250 words. Review Articles should not exceed 3,000 words. Commentaries should be between 750 and 1,000 words. Other kinds of original essays should not exceed 2,000 words. A letter of inquiry should be sent to the editor prior to submitting a Review Article or Commentary.

For Research Papers only, scientific measurements should be given in conventional units, with Système Internationale (SI) units in parentheses. Abbreviations and acronyms should be kept to a minimum, and jargon should be avoided. Generic names of drugs should be used instead of brand names.

FIGURES

The submission of color illustrations or slides is discouraged. Only black and white glossy photographic prints or "camera-ready" artwork will be accepted. The *Journal* is unable to provide art services such as the addition of arrows to photographs. A signed consent for publication must accompany photographs in which the patient is identifiable. Illustrations from other publications generally will not be considered. Legends for illustrations should be typed on a separate sheet, and for photomicrographs should include magnification and stain. Each illustration should be lightly marked on the back in pencil with the name of the first author, the number as cited in the text, and an arrow indicating the top. Each set of illustrations should be submitted unmounted in a separate envelope.

Tables should be simple, self-explanatory, and few in number. Each table should be typed double-spaced on a separate sheet.

REFERENCES

References should be limited to the most pertinent. The recommended maximum number of references is 25 for Research Papers and most other original contributions (except lengthier Review Articles), 12 for Commentaries and Case Reports, and six for letters to the editor.

Authors are responsible for the accurate citation of references. Citation of secondary sources is discouraged except where the original reference is unobtainable. Authors may not cite references they have not read, and the use of abstracts as references should be avoided.

References should be indicated in the text by superscript numbers following the name of the author (eg, Smith^2 reported two cases).

The list of references at the end of the article should be typed double-spaced and references should be numbered in the order in which they appear on the text. When there are six or fewer authors, all should be listed; where there are seven or more, the first three should be listed, followed by *et al.* Names of journals should be abbreviated according to *Index Medicus* and underlined.

Sample references:

1. Kepes ER, Thomas P, Vemulapalli K: Methadone and intravenous morphine requirements. *NY State J Med* 1983; 83:925–927.
2. McGuigan JE. Peptic ulcer. In: Petersdorf RG, Adams RD, Braunwald E, Isselbacher KJ, Martin JB, Wilson JD, eds. *Harrison's Principles of Internal Medicine.* New York, McGraw-Hill, 1983, pp 1697–1712.

REVIEW

All manuscripts are reviewed by the editors, and most manuscripts are sent to outside referees. Decisions concerning acceptance, revision, or rejection of a manuscript are usually made within three to six weeks. Every effort will be made to assure prompt publication of an accepted manuscript. A galley proof will be sent to the author for approval prior to publication.

Address correspondence to Alan Blum, MD, Editor, *New York State Journal of Medicine*, P.O. Box 5404, 420 Lakeville Road, Lake Success, NY 11042.

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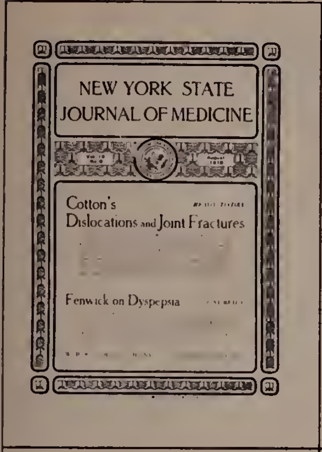
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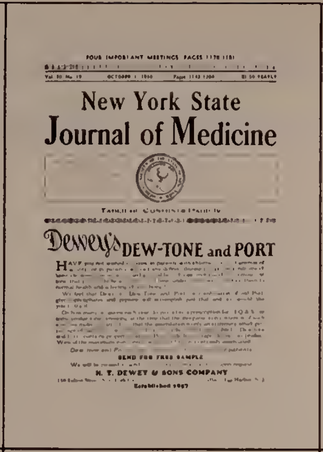
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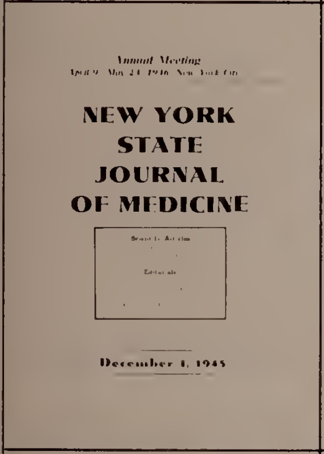
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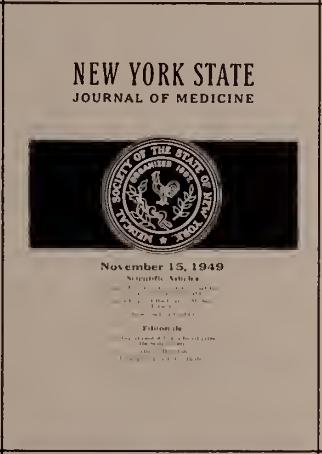
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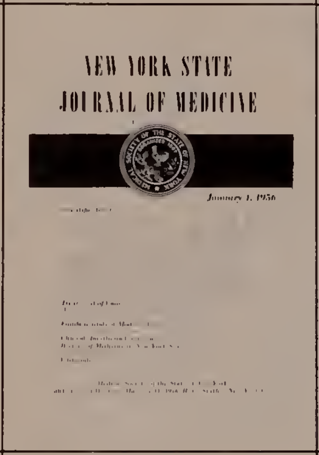
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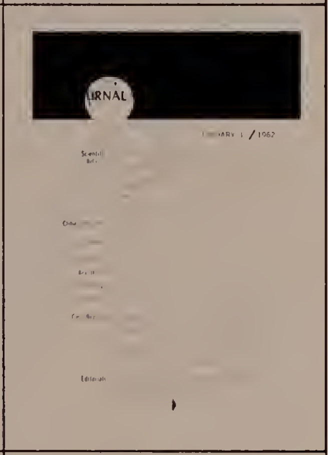

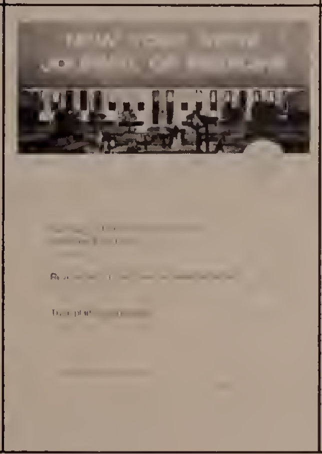

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Nov 13–16. **Procedure in Emergency Life Support.** Syracuse. *Nov 30–Dec 1.* **Postgraduate Course in Ophthalmology.** Hotel Syracuse. Info: Office of Continuing Education, SUNY Upstate Medical Center, 766 Irving Ave, Syracuse, NY 13210. Tel: (315) 473-5253.

ROCKLAND

Nov 6. **First Line Therapy for Arthritis in the 80s.** 1 Cat 1 credit. *Nov 13.* **Diagnosis & Treatment of Muscular Diseases.** 1 Cat 1 credit. *Nov 20.* **Treatment of the Vasculitides.** 1 Cat credit. *Nov 27.* **Steroid Induced Osteoporosis in the Rheumatoid Patient.** 1 Cat 1 credit. Nyack. Info: Mrs Myrna Hahn, Nyack Hospital, N. Midland Ave, New York, NY 10960. Tel: (914) 358-6200, ext 2509.

WESTCHESTER

Nov 7. **Alcoholism.** 6 Cat 1 credits. *Nov 28.* **Diabetes Day 1984.** 6 Cat 1 credits. White Plains. Info: Toni Calabrese Boelsen, White Plains Hospital Medical Center, Davis Ave, White Plains, NY 10601. Tel: (914) 681-1118.

AROUND THE NATION

ARIZONA

Nov 12–14. **Priorities in the Management of the Critically-Ill, Multi-Trauma Patient.** 16½ Cat 1 credits. Phoenix. Info: International College of Surgeons, United States Section, 1516 North Lake Shore Drive, Chicago, IL 60610.

CALIFORNIA

Nov 2–4. **Practical Endocrinology: Thyroid & Diabetes Workshop.** Berkeley. 17 Cat 1 credits. Info: University of California Extended Programs in Medical Education, Room 569-U, San Francisco, CA 94143. Tel: (415) 666-5808.

Nov 16–18. **Pulmonary Medicine & Office Spirometry for the Primary Care Physician.** 19 Cat 1 credits. San Diego, California. Info: Office of CME, UC San Diego School of Medicine, M-017, La Jolla, CA 92093. Tel: (619) 452-3940.

DISTRICT OF COLUMBIA

Nov 24. **Magnetic Resonance Imaging and Spectroscopy.** 7 Cat 1 credits. Washington. Info: UC San Francisco Radiology Postgraduate Education, San Francisco, CA 94143. Tel: (415) 666-5731.

FLORIDA

Nov 5–9. **Internal Medicine Update '84.** 20 Cat 1 credits. Sarasota. Info: Office of Continuing Education, SUNY Upstate Medical Center, 766 Irving Ave, Syracuse, NY 13210. Tel: (315) 473-5253.

Continued on p 18A

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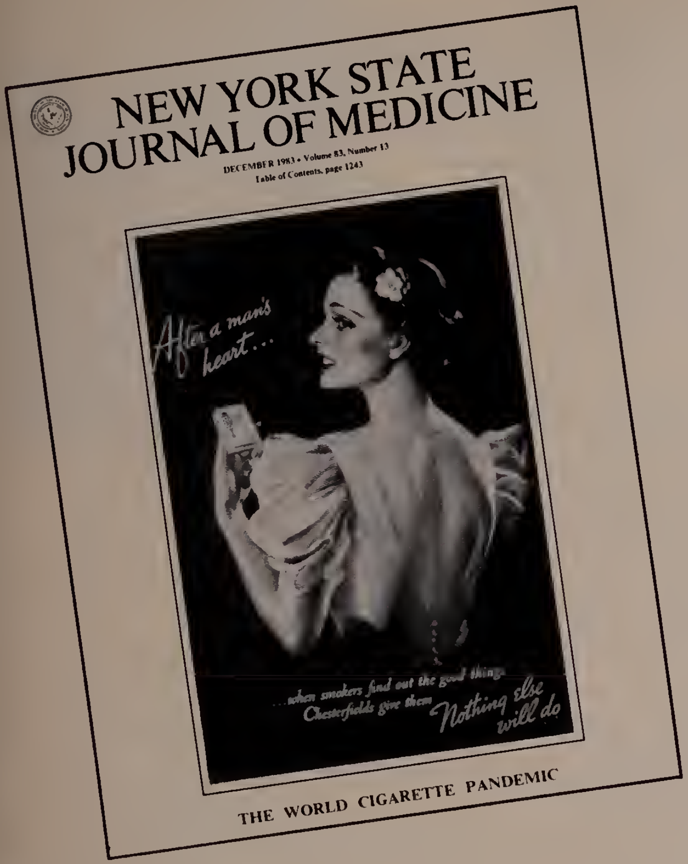

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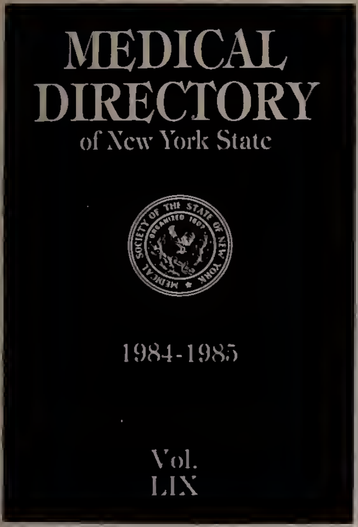

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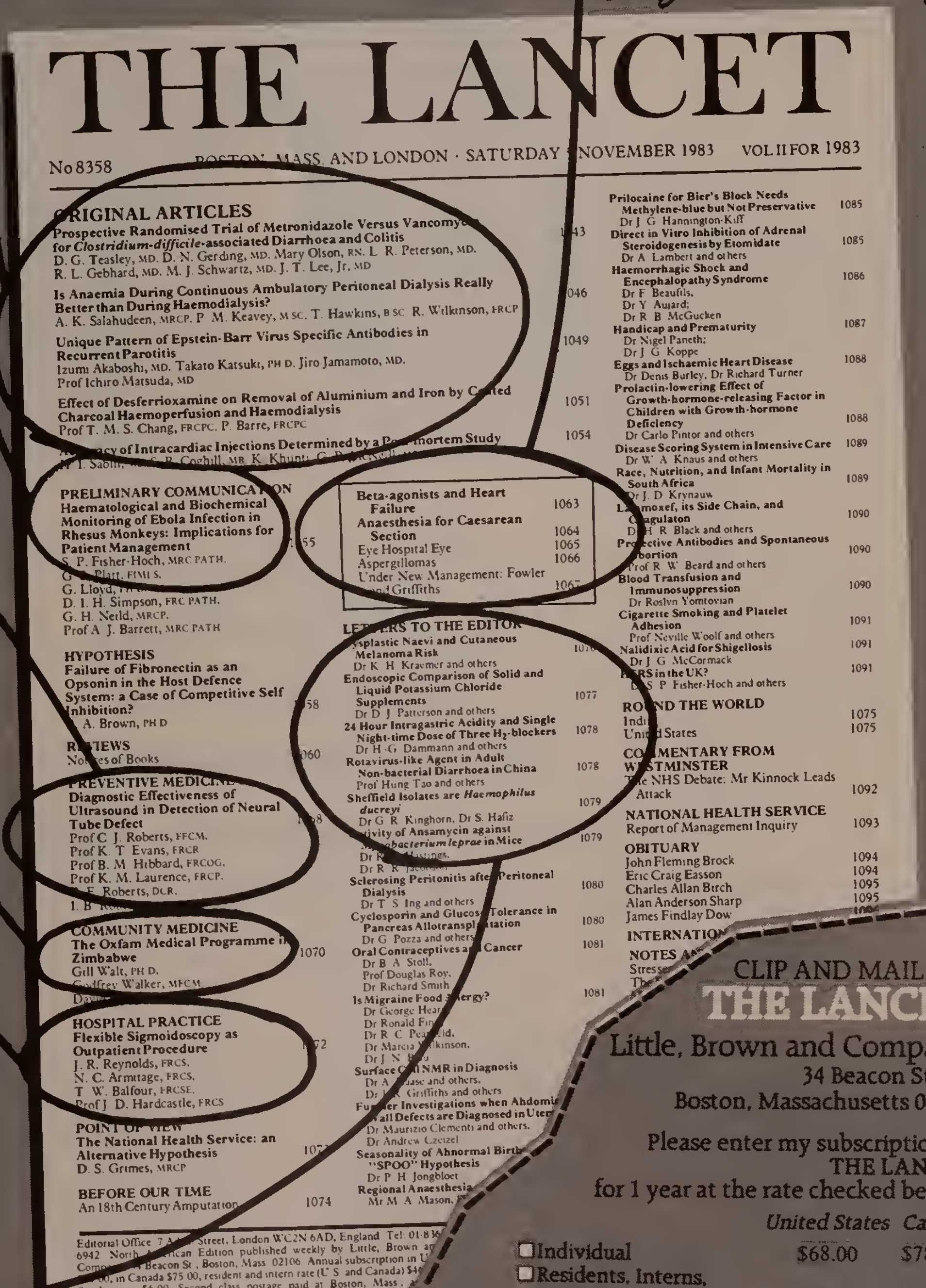

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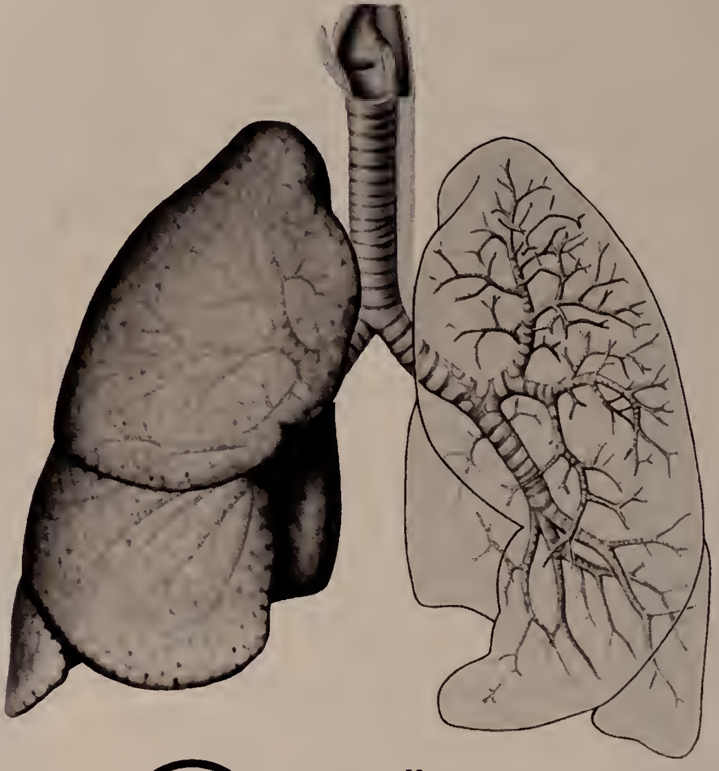

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Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins), therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics Such colitis may range in severity from mild to life-threatening

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation When the colitis does not improve after the drug has been discontinued, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C difficile* Other causes of colitis should be ruled out

Precautions: *General Precautions* – If an allergic reaction to Ceclor® (cefaclor, Lilly) occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e g , pressor amines, antihistamines, or corticosteroids

Prolonged use of Ceclor may result in the overgrowth of nonsusceptible organisms Careful observation of the patient is essential If superinfection occurs during therapy, appropriate measures should be taken

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug

Ceclor should be administered with caution in the presence of markedly impaired renal function Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly)

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis

Usage in Pregnancy – Pregnancy Category B – Reproduction studies have been performed in mice and rats at doses up to 12 times the human dose and in ferrets given three times the maximum human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Ceclor® (cefaclor, Lilly) There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Nursing Mothers – Small amounts of Ceclor have been detected in mother's milk following administration of single 500-mg doses Average levels were 0.18, 0.20, 0.21, and 0.16 mcg/ml at two, three, four, and five hours respectively Trace amounts were detected at one hour The effect on nursing infants is not known Caution should be exercised when Ceclor is administered to a nursing woman

Usage in Children – Safety and effectiveness of this product for use in infants less than one month of age have not been established

Adverse Reactions: Adverse effects considered related to therapy with Ceclor are uncommon and are listed below

Gastrointestinal symptoms occur in about 2.5 percent of patients and include diarrhea (1 in 70).

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment Nausea and vomiting have been reported rarely

Hypersensitivity reactions have been reported in about 1.5 percent of patients and include morbilliform eruptions (1 in 100) Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever) have been reported These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Ceclor Such reactions have been reported more frequently in children than in adults Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy No serious sequelae have been reported Antihistamines and corticosteroids appear to enhance resolution of the syndrome

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients)

Causal Relationship Uncertain – Transitory abnormalities in clinical laboratory test results have been reported Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician

Hepatic – Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic – Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal – Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200)

[061782R]

Note Ceclor® (cefaclor, Lilly) is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever See prescribing information

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12/10-12	321. Managing Clinical Problems in the Elderly
12/17-22	603. Computed Tomography (Grand Hyatt)
12/15-16	733. Basic Review of Pathology and Radiology for Urologists

JANUARY

1/9-6/26/85	302. Internal Medicine Board Review Wednesdays 4:00 to 7:00pm

MARCH

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3/11-15	603b. Computed Tomography (Cerromar Beach Hotel)
3/18-22	304. Seminar in Advanced Rheumatology
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Dosage may be increased to 160 mg once daily, as needed, to achieve optimal control. INDERAL LA should not be used in congestive heart failure, sinus bradycardia, cardiogenic shock, heart block greater than first degree, and bronchial asthma. Please see next page for further details and brief summary of prescribing information.

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BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)*
INDERAL® LA brand of propranolol hydrochloride **(Long Acting Capsules)**
DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.
CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity.

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain.

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.
INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.
CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first degree block; 3) bronchial asthma; 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.
WARNINGS. CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

> IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.
PRECAUTIONS. *General:* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.
ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia, congestive heart failure; intensification of AV block, hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia, visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.
DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized.* The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily.

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

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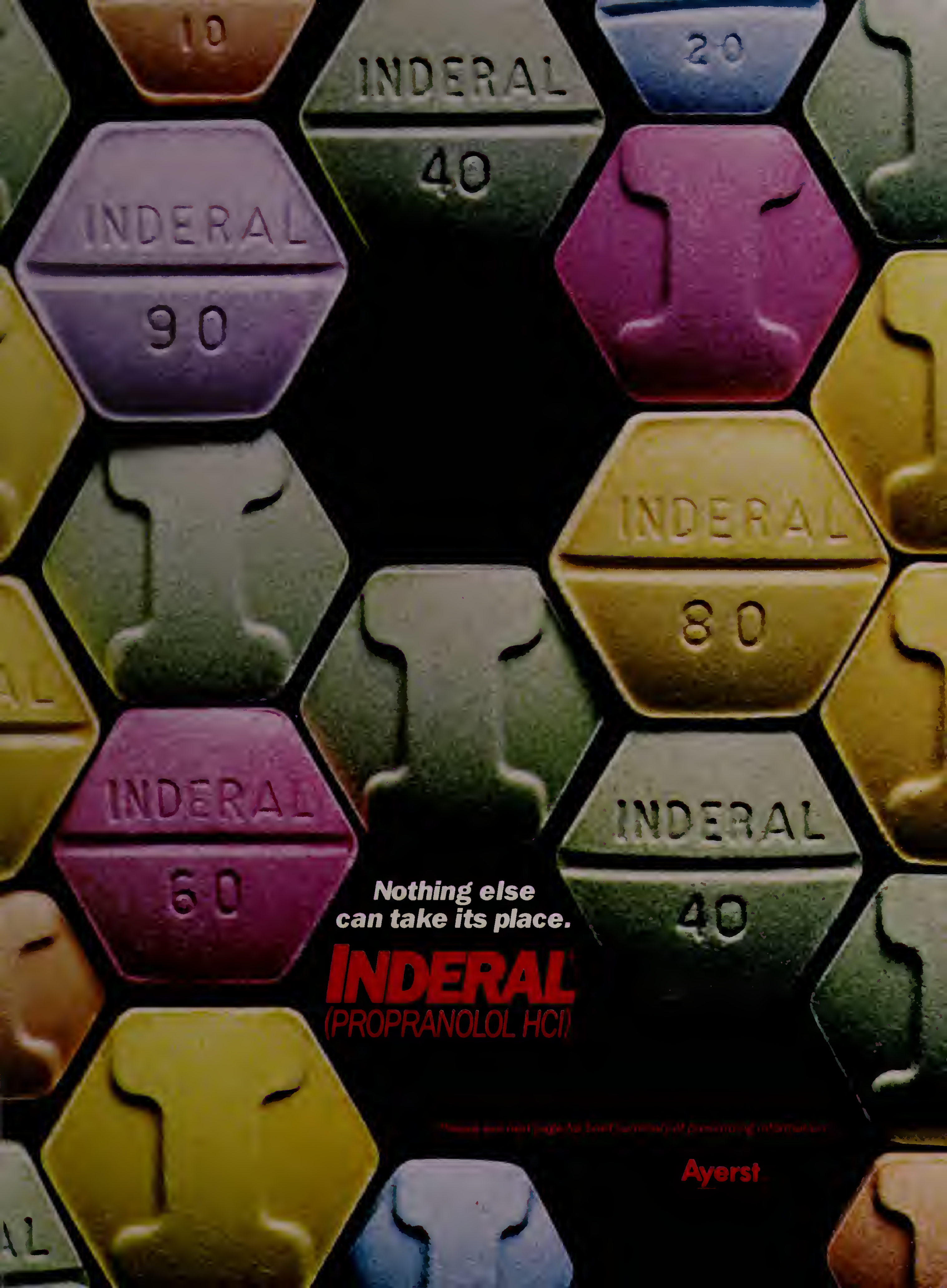
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Nothing else
can take its place.
INDERAL
(PROPRANOLOL HCl)
Please see next page for brief summary of prescribing information.
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Nothing else can take its place.

INDERAL®

(PROPRANOLOL HCl)

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR)

INDERAL® (propranolol hydrochloride) Tablets

CLINICAL PHARMACOLOGY

The Beta-Blocker Heart Attack Trial (BHAT) was a National Heart, Lung and Blood Institute-sponsored multicenter, randomized, double-blind placebo-controlled trial conducted in 31 U S centers (plus one in Canada) in 3,837 persons without history of severe congestive heart failure or presence of recent heart failure, certain conduction defects, angina since infarction, who had survived the acute phase of myocardial infarction Propranolol was administered at either 60 or 80 mg t i d based on blood levels achieved during an initial trial of 40 mg t.i.d Therapy with INDERAL, begun 5-21 days following infarction, was shown to reduce overall mortality up to 39 months, the longest period of follow-up This was primarily attributable to a reduction in cardiovascular mortality The protective effect of INDERAL was consistent regardless of age, sex or site of infarction Compared to placebo, total mortality was reduced 39% at 12 months and 26% over an average follow-up period of 25 months The Norwegian Multicenter Trial in which propranolol was administered at 40 mg q i d gave overall results which support the findings in the BHAT

Although the clinical trials used either t i d or q i d dosing, clinical, pharmacologic and pharmacokinetic data provide a reasonable basis for concluding that b i d dosing with propranolol should be adequate in the treatment of post-infarction patients

CLINICAL In the BHAT, patients on INDERAL were prescribed either 180 mg/day (82% of patients) or 240 mg/day (18% of patients) Patients were instructed to take the medication 3 times a day at mealtimes This dosing schedule would result in an overnight dosing interval of 12 to 14 hours which is similar to the dosing interval for a b i d regimen In addition, blood samples were drawn at various times and analyzed for propranolol When the patients were grouped into tertiles based on the blood levels observed and the mortality in the upper and lower tertiles were compared, there was no evidence that blood levels affected mortality

PHARMACOLOGIC Studies in normal volunteers have shown that a 90 mg b i d regimen maintains beta blockade at, or above, the minimum for 60 mg t i d dosing for 24 hours even though differences occurred at two time intervals At 10-12 hours after the first dose of the day, t i d dosing gave more beta blockade than b i d dosing, at 20-24 hours the trend of the relationship was reversed These relationships were similar in direction to those observed for plasma propranolol levels (see Pharmacokinetics)

PHARMACOKINETIC A bioavailability study in normal volunteers showed that the blood levels produced by 180 mg/day given b i d are below those provided by the same daily dosage given t i d at 10-12 hours after the first dose of the day but above those of a t i d regimen at 20-24 hours However the blood levels produced by b i d dosing were always equivalent to or above the minimum for t i d dosing throughout the 24 hours In addition, the mean AUC on the fourth day for the b i d regimen was about 17% greater than for the t i d regimen (1,194 vs 1,024 ng/ml•hr)

CONTRAINDICATIONS

INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL

WARNINGS

CARDIAC FAILURE Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure Although beta blockers should be avoided in overt congestive heart failure if necessary they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure Therefore at the first sign or symptom of heart failure the patient should be digitalized and/or treated with diuretics, and the response observed closely or INDERAL should be discontinued (gradually, if possible)

> IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction following abrupt discontinuance of INDERAL therapy Therefore when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks and the patient should be cautioned against interruption or cessation of therapy without the physician's advice If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS INDERAL (propranolol hydrochloride) should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors

MAJOR SURGERY The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e g , dobutamine or isoproterenol However, such patients may be subject to protracted severe hypotension Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers

DIABETES AND HYPOGLYCEMIA. Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin

THYROTOXICOSIS Beta blockade may mask certain clinical signs of hyperthyroidism Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker In one case this resulted after an initial dose of 5 mg propranolol

PRECAUTIONS

General Propranolol should be used with caution in patients with impaired hepatic or renal function INDERAL is not indicated for the treatment of hypertensive emergencies

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure Patients should be told that INDERAL may interfere with the glaucoma screening test Withdrawal may lead to a return of increased intraocular pressure

Clinical Laboratory Tests Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DRUG INTERACTIONS Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug

Pregnancy Pregnancy Category C INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose

There are no adequate and well-controlled studies in pregnant women INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Nursing Mothers INDERAL is excreted in human milk Caution should be exercised when INDERAL is administered to a nursing woman

Pediatric Use Safety and effectiveness in children have not been established

ADVERSE REACTIONS

Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy

Cardiovascular bradycardia, congestive heart failure, intensification of AV block, hypotension, paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type

Central Nervous System Lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis

Allergic pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress

Respiratory bronchospasm

Hematologic agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Auto-Immune In extremely rare instances, systemic lupus erythematosus has been reported

Miscellaneous alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

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Angina Protection with Benefits for a Lifetime

ONCE-DAILY CONTROL WITH HEART-SAVING BENEFITS

By reducing heart rate and cardiac contractility, INDERAL LA helps protect the heart from the potentially serious and debilitating consequences of ischemia. A highly effective antianginal agent for around-the-clock control of symptoms, INDERAL LA also provides cardiovascular protection for a sense of security in the years ahead.

PROTECTION AND EXPERIENCE NO CALCIUM BLOCKER CAN MATCH

Unlike calcium blockers, INDERAL LA—either alone or with a nitrate—is recommended for early treatment of angina in the majority of patients. Equally important, INDERAL LA delivers the proven performance and safety profile of INDERAL tablets—confirmed by millions of patients during 16 years of clinical use.

START WITH 80 MG ONCE DAILY

Dosage may be increased to 160 mg once daily, as needed, to achieve optimal control. INDERAL LA should not be used in congestive heart failure, sinus bradycardia, cardiogenic shock, heart block greater than first degree, and bronchial asthma. Please see next page for further details and brief summary of prescribing information.

ONCE-DAILY **INDERAL LA**
(PROPRANOLOL HCl) *LONG ACTING CAPSULES*

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JUST ONCE EACH DAY FOR SIMPLIFIED CORE THERAPY IN ANGINA

ONCE-DAILY INDERAL® LA

(PROPRANOLOL HCl) LONG ACTING CAPSULES

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)*
INDERAL* LA brand of propranolol hydrochloride **(Long Acting Capsules)**
DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.
CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential The significance of the membrane action in the treatment of arrhythmias is uncertain

The mechanism of the antimigraine effect of propranolol has not been established Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain.

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable
INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension, it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary
CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL
WARNINGS. CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

> IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY. The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e g dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker In one case this resulted after an initial dose of 5 mg propranolol
PRECAUTIONS. *General:* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure Patients should be told that INDERAL may interfere with the glaucoma screening test Withdrawal may lead to a return of increased intraocular pressure

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug

Pregnancy Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose There are no adequate and well-controlled studies in pregnant women INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Nursing Mothers: INDERAL is excreted in human milk Caution should be exercised when INDERAL is administered to a nursing woman

Pediatric Use: Safety and effectiveness in children have not been established
ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block, hypotension; paresthesia of hands; thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia, visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.
DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval

HYPERTENSION—*Dosage must be individualized* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved The usual maintenance dosage is 120 to 160 mg once daily In some instances a dosage of 640 mg may be required The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks

ANGINA PECTORIS—*Dosage must be individualized*. Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS)

MIGRAINE—*Dosage must be individualized* The initial oral dose is 80 mg INDERAL LA once daily The usual effective dose range is 160-240 mg once daily The dosage may be increased gradually to achieve optimum migraine prophylaxis If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued It may be advisable to withdraw the drug gradually over a period of several weeks

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily
PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use

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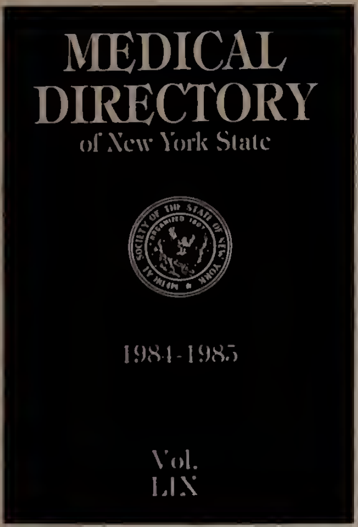

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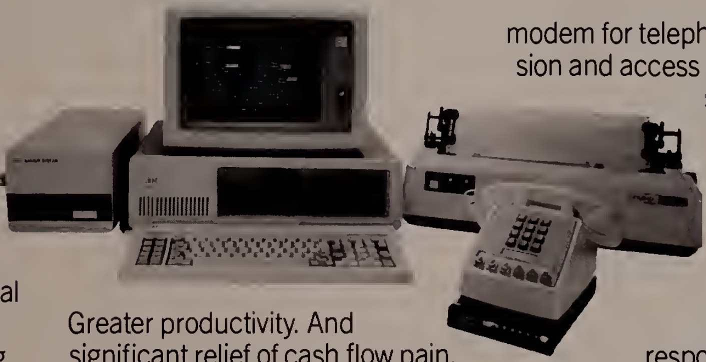

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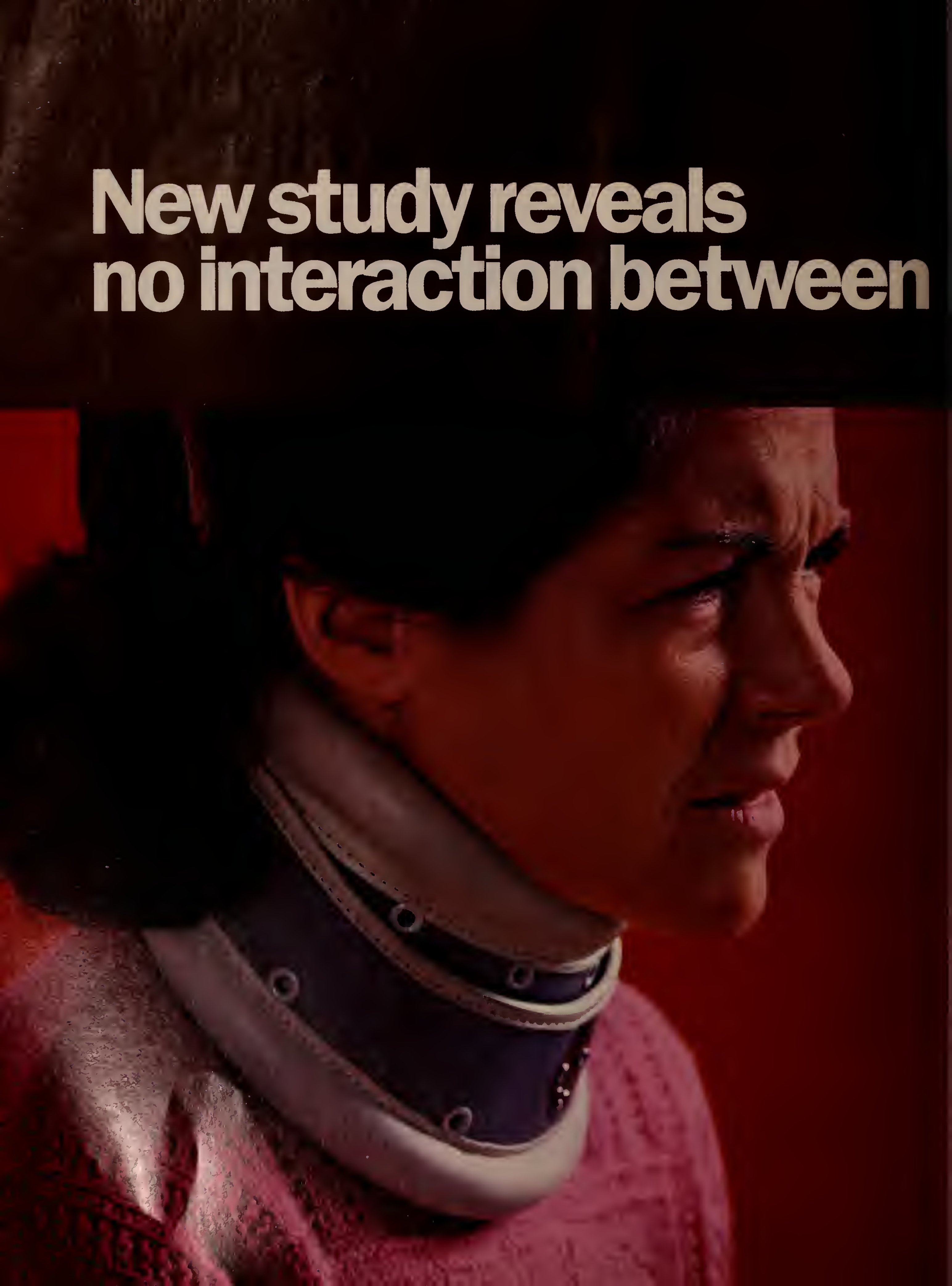
New study reveals
no interaction between

Ativan® (lorazepam) and Darvon® (propoxyphene HCl) Ⓒ

In a study evaluating the influence of propoxyphene coadministration on the pharmacokinetics of the oxidatively metabolized benzodiazepines Xanax® (alprazolam) Ⓒ and Valium® (diazepam) Ⓒ, and a benzodiazepine metabolized by conjugation, Ativan® (lorazepam), the following results were reported:

with Xanax, propoxyphene caused a large and highly significant prolongation of half-life and impairment of total metabolic clearance.[1]

in the case of Valium, propoxyphene produced a small but not statistically significant impairment of clearance.[1]

propoxyphene had no apparent effect on the distribution, half-life or clearance of Ativan.[1]

In this randomized crossover study, eight healthy male and female volunteers received single oral doses of alprazolam (1 mg), six received single IV doses of diazepam (10 mg), and five received single IV doses of lorazepam (2 mg), once in a drug-free control state and again during coadministration of propoxyphene (65 mg q6h). Consistent with previous findings, this study evidences that Ativan does not interact with drugs that undergo oxidative metabolism.[2-5] In contrast to most other benzodiazepines, Ativan does not compete for the cytochrome P-450 enzyme system.

The clinical implications of the pharmacokinetic interaction, or non-interaction, of propoxyphene with benzodiazepines are not established by this study. Even without a pharmacokinetic interaction, propoxyphene and benzodiazepines share central depressant properties and therefore should be coadministered with suitable caution. A concurrent pharmacokinetic interaction indicates a need for even further caution. Coadministration of propoxyphene and alprazolam, for example, would produce not only the expected pharmacodynamic interaction, but also whatever additional central depressant effect would be produced by the elevated steady-state plasma concentrations of alprazolam due to its impaired clearance.

Caution should also be observed when propoxyphene is prescribed for patients who use alcohol to excess.

References

1. Abernethy DR, Greenblatt DJ, Shader RI: Data on file, Wyeth Laboratories.
2. Patwardhan RV, Yarborough GW, Desmond PV, et al: Gastroenterology *79*:912-916, 1980.
3. Abernethy DR, Greenblatt DJ, Divoll M, et al: Psychopharmacology *80*:275-278, 1983.
4. Abernethy DR, Greenblatt DJ, Divoll M, et al: N Engl J Med *306*:791-792, 1982.
5. Ochs HR, Greenblatt DJ, Abernethy DR: Data on file, Wyeth Laboratories.

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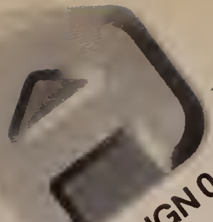
Ativan® for (lorazepam) Ⓒ Anxiety

See important information on following page.



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Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

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Anxiety

DOSAGE: Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.

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MEETINGS AND LECTURES

The New York State Journal of Medicine *cannot guarantee publication of meetings and lectures unless the information is submitted at least two months prior to the event.*

DECEMBER 1984

AROUND THE STATE

MANHATTAN

Dec 3–6. **Neurosurgery NYC-1984.** 25 Cat 1 credits. Grand Hyatt New York Hotel. Info: NYU Post-Graduate Medical School, 550 First Ave, New York, NY 10016. Tel: (212) 340-5295.

Dec 3–7. **Clinical Pharmacology & Toxicology: The Use, Misuse & Abuse of Drugs.** 27 Cat 1 credits. Info: NYU Post-Graduate Medical School, 550 First Ave, New York, NY 10016. Tel: (212) 340-5295.

Dec 4. **Thermography & Other Advances in Differential Diagnosis of Pain & Soft Tissue Pathology.** *Dec 5–7.* **Special Pathology Update: 1984.** 16 Cat 1 credits. *Dec 8.* **Psychopharmacology for Psychotherapists: New Developments.** Info: Page & William Black Post-Graduate School of Medicine, Mount Sinai Medical Center, One Gustave L. Levy Place, New York, NY 10029. Tel: (212) 650-6737.

Dec 6. **Integrated Care of the Chronic Disease Patient.** Roosevelt Island. Info: Susan M. Schnall, Coler Memorial Hospital, New York City Health and Hospitals Corporation, Roosevelt Island, NY 10044. Tel: (212) 688-9400.

Dec 6–9. **Psychoanalysis: Social, Moral and Political Influences.** Roosevelt Hotel. Info: Vivian Mendelsohn, The American Academy of Psychoanalysis, 30 E. 40 St, Ste 608, New York, NY 10016. Tel: (212) 679-4105.

Dec 7. **Language and Learning Disabilities in Speech & Hearing Handicapped School Children.** New York City Dept of Health, 455 First Ave. Info: Linda Steinhart, CNY Dept of Health, Bureau for Handicapped Children, 280 Broadway, New York, NY 10007. Tel: (212) 566-2181.

Dec 8. **Symposium of the Semmelweis-Virchow-Pirquet Medical Society—New Developments in Diabetes.** 8 Cat 1 credits. NY Academy of Medicine. Info: Dr Otto C. Kestler, NY Academy of Medicine, 2 E. 103 St, New York, NY 10029. Tel: (212) 876-8200.

Dec 10–12. **Managing Clinical Problems in the Elderly.** 20 Cat 1 credits. Info: NYU Post-Graduate Medical School, 550 First Ave, New York, NY 10016. Tel: (212) 340-5295.

Dec 15–16. **Basic Review of Pathology & Radiology for Urologists.** 14 Cat 1 credits. Info: NYU Post-Graduate Medical School, 550 First Ave, New York, NY 10016. Tel: (212) 340-5295.

Dec 17–22. **Computed Tomography Head to Toe.** 37 Cat 1 credits. Grand Hyatt New York Hotel. Info: NYU Post-Graduate Medical School, 550 First Ave, New York, NY 10016. Tel: (212) 340-5295.

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Dec 7 & 8. **Advanced Trauma Life Support.** Info: William M. Stahl, MD, Lincoln Medical Mental Health Center, 234 East 149th St, Bronx, NY 10451. Tel: (212) 579-5000.

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Dec 10. **Pharmacokinetics in Anesthesia: Concepts & Applications.** 1 Cat 1 credit. *Dec 11.* **Pharmacokinetics of Narcotics, New Concepts.** 1 Cat 1 credit. Info: Abraham I. Raskob, MD, SUNY—Downstate Medical Center, Dept of Anesthesiology, Box 6, 450 Clarkson Ave, Brooklyn, NY 11203. Tel: (212) 270-1934.

NASSAU

Dec 6. **Non-Edema Use of Diuretics.** 1 Cat 1 credit. *Dec 13.* **Visceral Manifestations of Rheumatoid Arthritis.** 1 Cat 1 credit. Info: Ethel A. Ford, CME Coordinator, Department of Medicine, Nassau County Medical Center, 2201 Hempstead Turnpike, East Meadow, NY 11554. Tel: (516) 542-0123.

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Dec 13. **Sexual Issues in Medicine.** 1 Cat 1 credit. Rhinebeck. Info: Vivian Cadbury, Medical Staff Coordinator, Northern Dutchess Hospital, Rhinebeck, NY 12572. Tel: (914) 876-3001.

ERIE

Dec 6. **Lung Cancer: Problems and What's New.** 4 Cat 1 credits. Buffalo. Info: Gayle Bersani, RN, Education Coordinator, Rosewell Park Memorial Institute, 666 Elm St, Buffalo, NY 14263. Tel: (716) 845-2339.

ROCKLAND

Dec 4. **Calcium Metabolism and Treatment of Hypercalcemia.** 1 Cat 1 credit. Nyack. Info: Mrs. Myrna Hahn, Nyack Hospital, N. Midland Ave, Nyack, NY 10960. Tel: (914) 358-6200, ext 2509.

AROUND THE NATION

CALIFORNIA

Dec 3–7. **Fundamental Techniques of Microsurgery.** 34 Cat 1 credits. University Hospital & Medical Center, San Diego. Info: Office of CME, University of California, San Diego School of Medicine, (M-017), La Jolla, CA 92093. Tel: (619) 452-3940.

Dec 7–8. **Cancer Prevention—Strategies in the Workplace.** Sir Francis Drake Hotel. 14 Cat 1 credits. Info: Extended Programs in Medical Education, University of California at San Francisco, Room 569-U, San Francisco, CA 94143. Tel: (415) 666-4251.

FLORIDA

Dec 6–8. **Clinical Allergy & Immunology for the Practicing Physician.** Lake Buena Vista. Info: Mary Fogarty, The American Academy of Allergy & Immunology, 611 East Wells St, Milwaukee, WI 53202. Tel: (414) 272-6071.

Dec 12–18. **Emergencies in Internal Medicine VII.** 34 Cat 1 credits. St. Thomas, US Virgin Islands. Info: Div of CME, D23-3 Univ of Miami School of Medicine, PO Box 016960, Miami, FL 33101. Tel: (305) 547-6716.

KANSAS

Dec 3–4. **Incest: The Offender and the Offense.** 12 Cat 1 credits, Topeka. Info: Div of Continuing Education, The Menninger Foundation, Box 829, Topeka, KS 66601. Tel: (913) 273-7500, Ext 5992.

NEW JERSEY

Dec 6–7. **Pediatric Decemberfest.** 10 Cat 1 credits. Atlantic City. Info: Office of CME, Temple University School of Medicine, 3400 North Broad Street, Philadelphia, PA 19140. Tel: (215) 221-4787.

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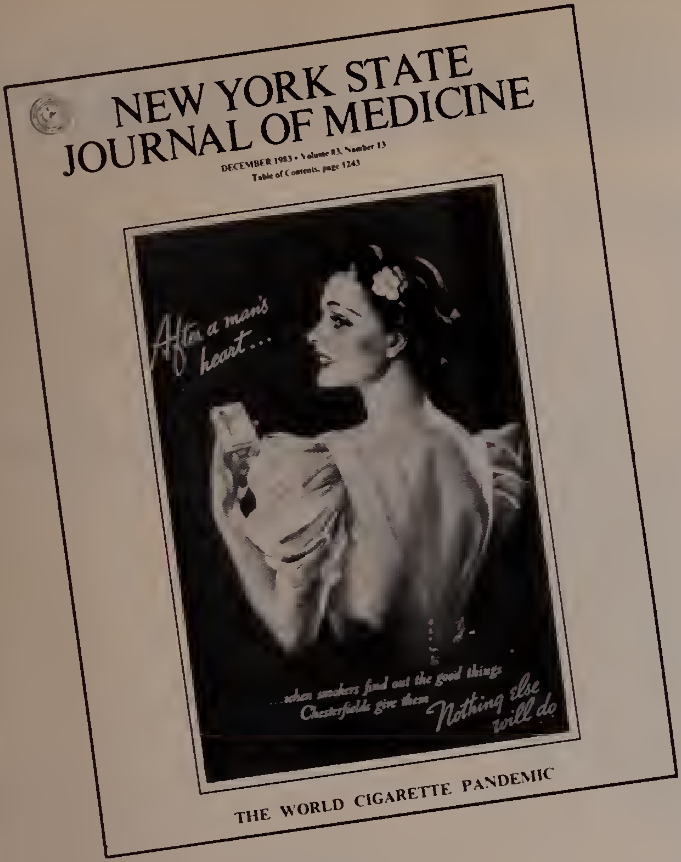
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See next page for references and summary of product information.

References: **1**. Kales J *et al: Clin Pharmacol Ther 12*:691-697, Jul-Aug 1971 **2**. Kales A *et al: Clin Pharmacol Ther 18*.356-363, Sep 1975. **3**. Kales A *et al Clin Pharmacol Ther 19* 576-583, May 1976. **4**. Kales A *et al Clin Pharmacol Ther 32*:781-788, Dec 1982. **5**. Frost JD Jr, DeLucchi MR: *J Am Geriatr Soc 27*:541-546, Dec 1979. **6**. Kales A, Kales JD: *J Clin Pharmacol* 3:140-150, Apr 1983. **7**. Monti JM *Methods Find Exp Clin Pharmacol* 3:303-326, May 1981. **8**. Greenblatt DJ *et al: Sleep* 5 (Suppl 1):S18-S27, 1982. **9**. Kales A *et al: Pharmacology* 26.121-137, 1983. **10**. Greenblatt DJ, Allen MD, Shader RI: *Clin Pharmacol Ther 21*:355-361, Mar 1977. **11**. Zimmerman AM: *Curr Ther Res 13*:18-22, Jan 1971 **12**. Amrein R *et al: Drugs Exp Clin Res* 9(1):85-99, 1983.

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Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. An additive effect may occur if alcohol is consumed the day following use for nighttime sedation. This potential may exist for several days following discontinuation. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving) Potential impairment of performance of such activities may occur the day following ingestion. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, abrupt discontinuation should be avoided with gradual tapering of dosage for those patients on medication for a prolonged period of time. Use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in severely depressed patients, or in those with latent depression or suicidal tendencies, or in those with impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported, headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins, and alkaline phosphatase; and paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity

Dosage: Individualize for maximum beneficial effect. *Adults*: 30 mg usual dosage 15 mg may suffice in some patients. *Elderly or debilitated patients*. 15 mg recommended initially until response is determined

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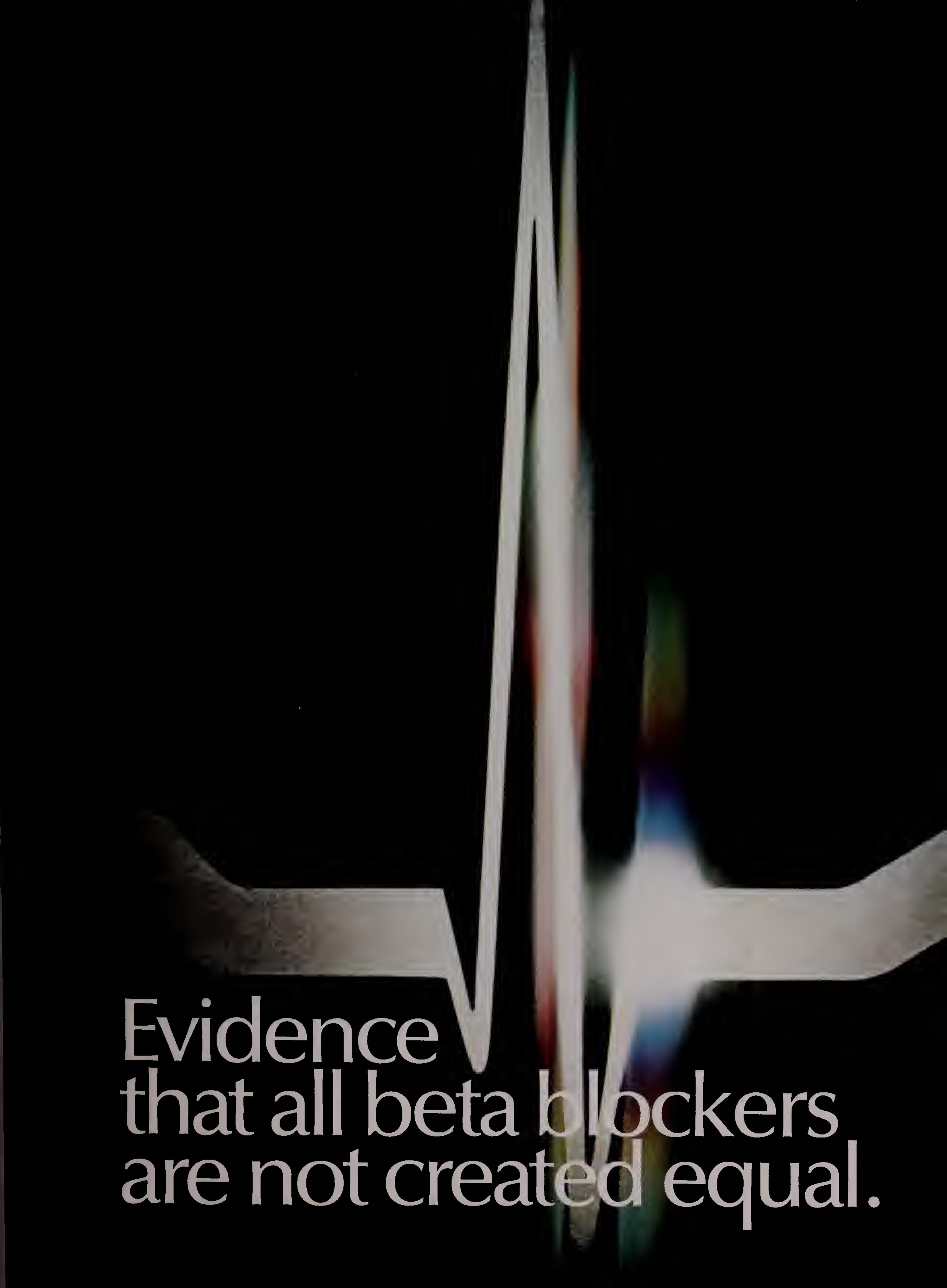

Evidence
that all beta blockers
are not created equal.

New studies uncover the potassium effects of beta-2 blockade

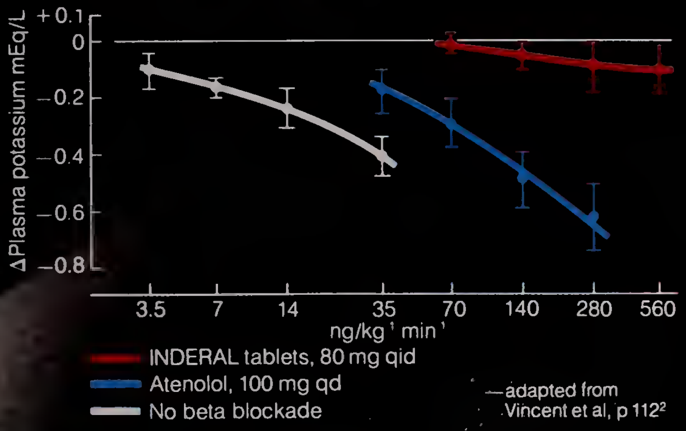
Clinical pharmacology data from the *New England Journal of Medicine:*

"...when normal young men are given infusions of epinephrine at levels such as those that circulate in patients with myocardial infarction, their serum potassium concentrations fall by about 0.8 mmol per liter. Hypokalemia is prevented by...beta-2 blockade."[1]

INDERAL (propranolol HCl) prevented beta-2 mediated hypokalemia

In a pharmacological study comparing INDERAL with atenolol, 10 hypertensive patients were infused with the nonselective beta agonist, isoproterenol, which also stimulates beta-2 mediated hypokalemia. At doses high enough to overcome beta-1 mediated heart rate reductions, the hypokalemia caused by isoproterenol was blunted by INDERAL, but not by atenolol.[2]

INDERAL compared with atenolol: change in plasma potassium after beta-agonist infusion[2]



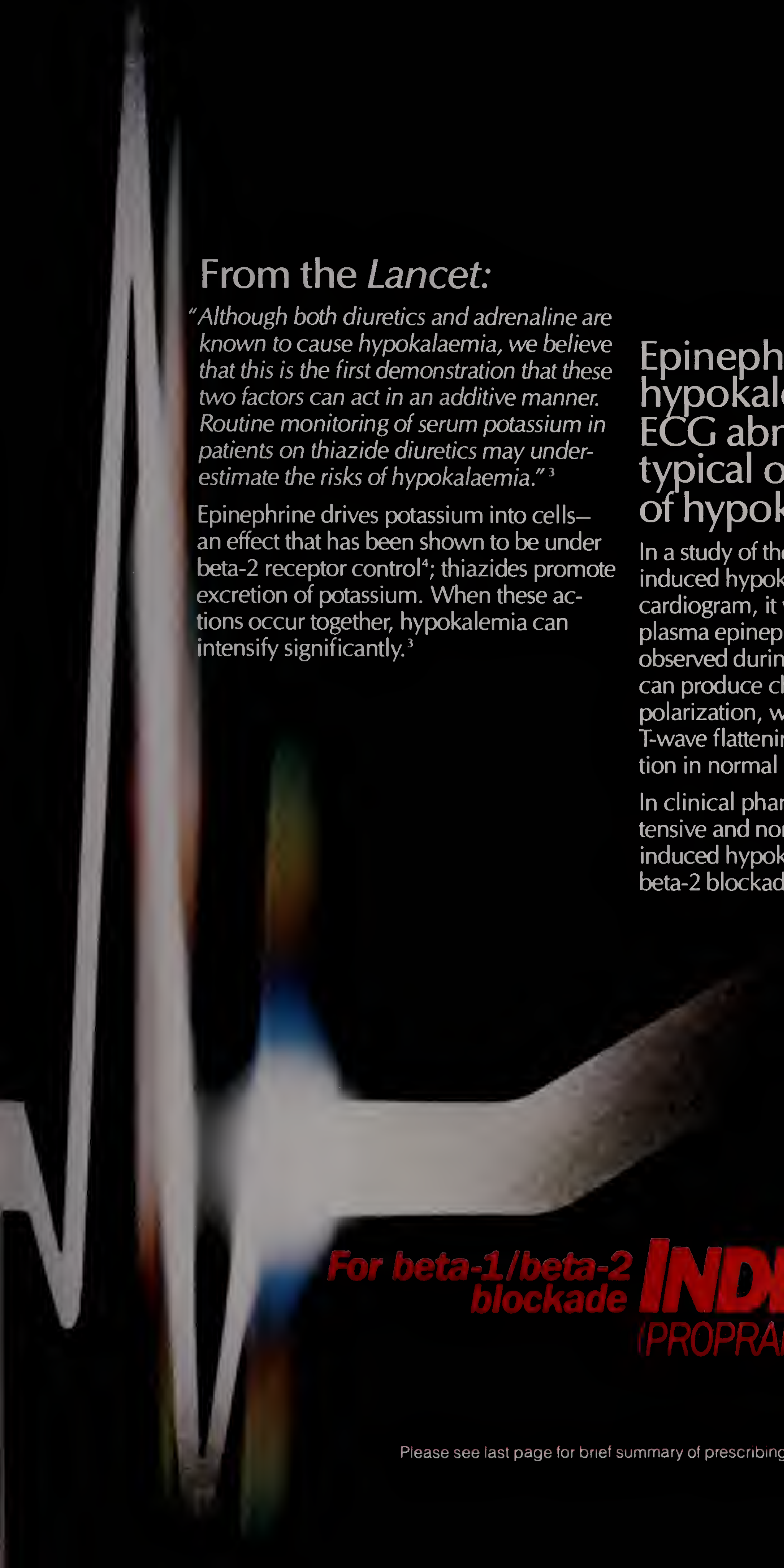
—adapted from Vincent et al, p 112[2]

For beta-1/beta-2 blockade INDERAL®

(PROPRANOLOL HCl) TABLETS

Please see last page for brief summary of prescribing information.

Epinephrine-induced hypokalemia can intensify diuretic-induced hypokalemia



From the *Lancet:*

"Although both diuretics and adrenaline are known to cause hypokalaemia, we believe that this is the first demonstration that these two factors can act in an additive manner. Routine monitoring of serum potassium in patients on thiazide diuretics may underestimate the risks of hypokalaemia." [3]

Epinephrine drives potassium into cells—an effect that has been shown to be under beta-2 receptor control[4]; thiazides promote excretion of potassium. When these actions occur together, hypokalemia can intensify significantly.[3]

Epinephrine-induced hypokalemia can cause ECG abnormalities typical of other forms of hypokalemia

In a study of the effects of epinephrine-induced hypokalemia on the electrocardiogram, it was shown that levels of plasma epinephrine similar to those observed during myocardial infarction can produce changes in ventricular repolarization, which are reflected in T-wave flattening and QT prolongation in normal subjects.[5]

In clinical pharmacology studies of hypertensive and normal patients, epinephrine-induced hypokalemia was prevented by beta-2 blockade.[2,4]

For beta-1/beta-2 blockade INDERAL

(PROPRANOLOL HCl) TABLETS

Please see last page for brief summary of prescribing information.

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Patients with "uncomplicated" hypertension may develop ventricular arrhythmias in the presence of hypokalemia.[6] Once-daily INDERAL LA maintains smooth blood pressure reductions without a negative effect on serum potassium and provides patients with broad cardiovascular benefits—all in a convenient daily dose.

Like conventional INDERAL tablets, INDERAL LA should not be used in the presence of congestive heart failure, sinus bradycardia, heart block greater than first degree, and bronchial asthma.

And for lifetime benefits in foundation treatment of angina

Once-daily INDERAL LA provides 24-hour control of angina symptoms—plus the cardiovascular benefits of the world's leading beta blocker. And unlike calcium channel blockers, INDERAL LA, alone or with a nitrate, is recommended for first-line treatment of stable angina.

Simply start new patients on 80 mg INDERAL LA once daily. Dosage may be increased to 160 mg once daily to achieve maximal control.

Once-daily
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(PROPRANOLOL HCl) LONG ACTING CAPSULES
In HYPERTENSION
and ANGINA

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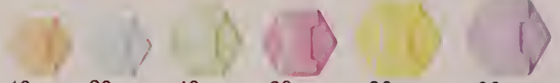
Please see last page for brief summary of prescribing information

80 mg 120 mg 160 mg

INDERAL®

(PROPRANOLOL HCl) TABLETS



10 mg 20 mg 40 mg 60 mg 80 mg 90 mg

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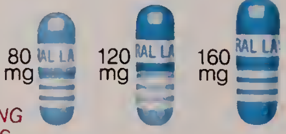
Once daily INDERAL® LA

(PROPRANOLOL HCl) LONG ACTING CAPSULES



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BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULARS.)*
INDERAL® (propranolol hydrochloride) **Tablets and Injectable**
INDERAL® LA (propranolol hydrochloride) **Long Acting Capsules**

INDICATIONS AND USAGE—INDERAL Tablets

Hypertension: INDERAL (propranolol hydrochloride) is indicated in the management of hypertension. It may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic INDERAL is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL is indicated for the long-term management of patients with angina pectoris.

Cardiac Arrhythmias:

1) Supraventricular arrhythmias

a) Paroxysmal atrial tachycardias, particularly those arrhythmias induced by catecholamines or digitalis or associated with the Wolff-Parkinson-White syndrome. (See W-P-W under WARNINGS.) b) Persistent sinus tachycardia which is noncompensatory and impairs the well-being of the patient. c) Tachycardias and arrhythmias due to thyrotoxicosis when causing distress or increased hazard and when immediate effect is necessary as adjunctive, short term (2-4 weeks) therapy May be used with, but not in place of, specific therapy (See Thyrotoxicosis under WARNINGS) d) Persistent atrial extrasystoles which impair the well-being of the patient and do not respond to conventional measures. e) Atrial flutter and fibrillation when ventricular rate cannot be controlled by digitalis alone, or when digitalis is contraindicated

2) Ventricular tachycardias

Ventricular arrhythmias do not respond to propranolol as predictably as do the supraventricular arrhythmias a)Ventricular tachycardias With the exception of those induced by catecholamines or digitalis, INDERAL is not the drug of first choice In critical situations when cardioversion technics or other drugs are not indicated or are not effective, INDERAL may be considered If, after consideration of the risks involved, INDERAL is used, it should be given intravenously in low dosage and very slowly (See DOSAGE AND ADMINISTRATION) *Care in the administration of* INDERAL *with constant electrocardiographic monitoring is essential as the failing heart requires some sympathetic drive for maintenance of myocardial tone.* b) Persistent premature ventricular extrasystoles which do not respond to conventional measures and impair the well-being of the patient

3) Tachyarrhythmias of digitalis intoxication

If digitalis-induced tachyarrhythmias persist following discontinuance of digitalis and correction of electrolyte abnormalities, they are usually reversible with *oral* INDERAL. Severe bradycardia may occur (See OVERDOSAGE) Intravenous propranolol hydrochloride is reserved for life-threatening arrhythmias. Temporary maintenance with oral therapy may be indicated (See DOSAGE AND ADMINISTRATION in the package circulars.)

4) Resistant tachyarrhythmias due to excessive catecholamine action during anesthesia

Tachyarrhythmias due to excessive catecholamine action during anesthesia may sometimes arise because of release of endogenous catecholamines or administration of catecholamines When usual measures fail in such arrhythmias, INDERAL may be given intravenously to abolish them. All general inhalation anesthetics produce some degree of myocardial depression. Therefore, when INDERAL (propranolol hydrochloride) is used to treat arrhythmias during anesthesia, it should be used with extreme caution and constant ECG and central venous pressure monitoring (See WARNINGS.)

Myocardial Infarction: INDERAL is indicated to reduce cardiovascular mortality in patients who have survived the acute phase of myocardial infarction and are clinically stable.

Migraine: INDERAL is indicated for the prophylaxis of common migraine headache The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use

Hypertrophic Subaortic Stenosis: INDERAL is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope INDERAL also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta receptor stimulation Clinical improvement may be temporary

Pheochromocytoma: After primary treatment with an alpha-adrenergic blocking agent has been instituted, INDERAL may be useful as *adjunctive* therapy if the control of tachycardia becomes necessary before or during surgery

It is hazardous to use INDERAL unless alpha-adrenergic blocking drugs are already in use, since this would predispose to serious blood pressure elevation. Blocking only the peripheral dilator (beta) action of epinephrine leaves its constrictor (alpha) action unopposed

In the event of hemorrhage or shock, there is a disadvantage in having both beta and alpha blockade since the combination prevents the increase in heart rate and peripheral vasoconstriction needed to maintain blood pressure.

With inoperable or metastatic pheochromocytoma, INDERAL may be useful as an adjunct to the management of symptoms due to excessive beta receptor stimulation

INDICATIONS AND USAGE—INDERAL LA Long Acting Capsules

Hypertension: INDERAL LA (propranolol hydrochloride) is indicated in the management of hypertension, it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope INDERAL LA also improves exercise performance The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation Clinical improvement may be temporary

CONTRAINDICATIONS. INDERAL and INDERAL LA are contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL

WARNINGS. CARDIAC FAILURE· Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

> IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL (propranolol hydrochloride) therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)— PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors

MAJOR SURGERY· The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures

INDERAL, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g , dobutamine or isoproterenol However, such patients may be subject to protracted severe hypotension Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers

DIABETES AND HYPOGLYCEMIA Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS· Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm Propranolol does not distort thyroid function tests

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker In one case this resulted after an initial dose of 5 mg propranolol

PRECAUTIONS. *General.* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies

Beta adrenoreceptor blockade can cause reduction of intraocular pressure Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility· Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity There were no drug-related tumorigenic effects at any of the dosage levels Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug

Pregnancy· Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Nursing Mothers: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System. Lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia, visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal· nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory· bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

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9410/1184

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NEW YORK STATE
JOURNAL OF MEDICINE

November 1984 • Volume 84, Number 11

COMMENTARIES

Autonomously functioning thyroid adenomas

Autonomously functioning thyroid adenomas are discrete, benign neoplasms of the thyroid that secrete thyroid hormone independent of pituitary control. They are relatively uncommon lesions, constituting 5% to 10% of all discrete thyroid nodules in the United States. They are somewhat more common in Europe. Autonomously functioning thyroid adenomas are usually grossly solitary, but on occasion two or more palpable lesions may be found in a single thyroid. More often there are impalpable foci of autonomous tissue elsewhere in the thyroid that may be identified by imaging or with radioautographs. Nontoxic autonomous thyroid adenomas outnumber the toxic form by 6 to 1. In the United States toxic autonomously functioning thyroid adenoma as a cause of hyperthyroidism is less common than toxic multinodular goiter by a factor of 5, and less common than Graves' disease by a factor of 80. In Europe, patients with toxic autonomously functioning thyroid adenoma constitute a much larger subpopulation of those with hyperthyroidism.

In the first two decades of this century, and even beyond, skepticism was rampant as to the existence of thyroid adenomas capable of secreting thyroid hormone in amounts adequate to produce toxicity. It had even been proposed that lesions, nonfunctional themselves, cause excess secretion of thyroid hormone by compressing adjacent thyroid tissue as they grew.

In this climate the pioneering work of Emil Goetsch is particularly notable.[1] Not only did he firmly establish the validity of the concept of the toxic adenoma, but, in 1918, he provided microscopic anatomical evidence for both functional autonomy and the principle of endocrine negative feedback autoregulation—fully 25 years before this idea gained general acceptance.

Goetsch observed that toxic adenomas were always associated with atrophic tissue elsewhere in the thyroid, even tissue remote from the toxic adenoma itself. Using cellular mitochondrial content as an index of function, he showed that the thyroid epithelial cells in patients with Graves' disease had greatly increased mitochondrial content, compared to cells from unaffected patients. A similar increase was observed in the cells from toxic adenomas; but nontoxic adenomas with similar histologic structure had few mitochondria. Even more important, in patients with toxic adenomas, the epithelial cells of the extranodular thyroid tissue were virtually devoid of mitochondria.

On the basis of these findings, Goetsch concluded that in the presence of a toxic adenoma there was no physiologic requirement for extranodular tissue hormonal secretion. Hence the extranodular tissue became inactive. As final proof of his theory he showed that excision of toxic adenomas led to restoration of the euthyroid state. His findings were quickly confirmed by others. However, this did not end the controversy over the existence of toxic adenomas. It was not until the availability of radioactive iodine that the issue was finally settled. Cope, in 1947, confirmed the findings of Goetsch, showing that as the radioactive iodine content of adenomas increased there was a corresponding decrease in the tracer uptake of the extranodular tissue.[2] These studies were confirmed with various types of imaging devices.[3,4]

Autonomously functioning thyroid adenomas are found in women 9 times as often as in men. About 33% of the lesions in men are toxic, about twice the frequency of toxicity in women.[5] Older patients are more likely to have toxic lesions; about 50% of the lesions in patients over 60 years old were toxic, compared to 12% for those between the ages of 20 and 60 years.[5] It has been said that autonomously functioning thyroid adenomas, especially the toxic form, are uncommon in teenagers.[6] However, 9% of the lesions encountered in my experience were in teenagers, almost all of them in females. Also, 14% of the lesions in teenagers were toxic. Most toxic autonomous thyroid adenomas were 3.0 cm in diameter or larger; about 20% of the nontoxic lesions that large became toxic within six years.[5] Smaller, nontoxic lesions seldom progressed to toxicity very rapidly.

Diagnosis of autonomously functioning thyroid adenoma is easily accomplished with modern tracer techniques. In the past it was thought that "hot" nodules might represent either an adenomatous lesion or examples of thyroid stimulating hormone-dependent compensatory hyperplasia. It is now appreciated that almost all such lesions are autonomous thyroid adenomas. Confirmatory imaging studies include stimulation or suppression procedures. If the lesion is a "hot" nodule with nearly complete absence of function in the contralateral lobe, a repeat image after thyroid stimulating hormone stimulation will show activation of extranodular tissue with an autonomously functioning thyroid adenoma, reflecting the preferential sensitivity of extranodular tissue to thyroid stimulating hormone. More often, the "hot" nodule will be found in a thyroid with considerable function in the extranodular tissue. In these cases the confirmatory study should be a suppression image performed on the last day of a five to seven day period of treatment with triiodothyronine (T_3), 50 μg twice a day. If the lesion is an autonomously functioning thyroid adenoma, it will remain "hot" on the suppression image, while the extranodular tissue exhibits preferential suppressibility of function. If confirmatory stimulation or suppression images are not done as described above, misleading results may be obtained.

The old T_3 suppression test is seldom useful, and may give misleading information. For example, even in the presence of an autonomous thyroid adenoma, there may be a sharp drop in the radioactive iodine uptake on T_3 administration in patients in whom there is coincidental tracer uptake by extranodular tissue. It is the extranodular tissue uptake that has been suppressed. The suppression image is the appropriate diagnostic test.

The diagnosis of an autonomous thyroid adenoma is made by imaging techniques. The determination of the functional activity is based upon clinical evaluation, with confirmation by in vitro studies. Usually the serum T_3 level becomes elevated before the serum thyroxine (T_4) level. Also, in lesions that are approaching toxicity a blunted response to thyrotropin releasing hormone testing is seen. When hyperthyroidism is overt, the diagnosis is straightforward. The more challenging problem is to establish that toxicity is impending, for this may indicate that prophylactic therapy is prudent. Findings suggestive of impending toxicity include a lesion 3.0 cm or larger, in a patient older than 60, especially a man; finding on imaging of a "hot" nodule with complete or nearly complete suppression of extranodular tissue function; a serum T_3 level that is at the higher end of the normal range or slightly elevated; and a blunted response to thyrotropin releasing hormone testing. The greater the number of these findings present, the greater the risk of toxicity in the near future, and the stronger the case for prophylactic treatment.

Most non-toxic autonomously functioning thyroid adenomas remain relatively stable in size and secretory activity on follow-up examination for many years. Spontaneous degeneration occurs in most lesions as they enlarge beyond 1.5 to 2.0 cm in diameter. This process is most often gradual, but occasionally may be quite sudden in onset, with expansion of the nodule by hemorrhage; this can cause infarction of much of the parenchymal tissue. In some instances this may lead to disruption of follicles and discharge of preformed thyroid hormone into the circulation to produce hyperthyroidism[7]—a process very similar to that seen in subacute granulomatous thyroiditis. The hyperthyroidism resolves spontaneously as the discharged hormone is metabolized. If extensive, this process may lead to what is essentially an autoablation of the nodule, converting what had been a "hot" nodule to a "cold" nodule. Often, however, some functioning parenchyma persists. Depending on the amount of persistent autonomously functioning tissue that remains, the prospect for future toxicity may be more or less eliminated.

Recent studies have shown that progress from a nontoxic to a toxic lesion is neither rapid nor common in most cases.[5] It is more likely if the lesion is approaching the level of toxicity when the patient is first seen. Small autonomously functioning thyroid adenomas (1.0 to 1.5 cm) seldom progress to toxicity within 5 to 10 years. Because stability or spontaneous degeneration are the more common courses for nontoxic lesions, prophylactic ablative therapy is generally unnecessary.

The development of toxicity in a patient with an autonomous thyroid adenoma may not mean that the lesion has become hyperthyroid spontaneously. Before drawing that conclusion one must exclude three other possibilities. First, exposure to iodine in high concentration—in medication or radiographic contrast media—can convert a nontoxic lesion to a toxic lesion. Second, spontaneous hemorrhagic infarction can cause transient hyperthyroidism. This process is usually painless. A sudden enlargement of the nodule, with a change in the image to one of a partially or predominantly "cold" lesion provides further support for that diagnosis. Needle aspiration will produce blood and lead to collapse of the nodule. Finally, the unexpected administration of thyroid hormone can cause toxicity, even if in usual replacement doses, because the exogenous hormone will be additive to the endogenous, autonomous secretion. Thyroid hormone may be given by "diet doctors," because of erroneous or misleading laboratory data—low T_3 resin uptake values in women taking birth control medication or other forms of female hormone, for example—or in a misguided attempt at shrinking the nodule by a physician who does not understand the underlying pathophysiology. Of course, one must always be on the alert for factitious self administration of thyroid hormone.

The report of Leonidas and Schussler[8] in this issue of the *Journal* of a patient who had an autonomously functioning thyroid adenoma that became transiently toxic, and after a period of euthyroidism had a recurrence of toxicity that again remitted after a few months' treatment with propylthiouracil, raises important questions. The first of the two episodes of hyperthyroidism might be explained on the basis of intercurrent hemorrhagic partial degeneration, with subsequent recovery of function. Lack of pain does not exclude this diagnosis, since in most instances hemorrhagic infarction is painless. Nor is a persistent "hot" nodule convincing evidence against hemorrhagic infarction, for there might have been anterior and posterior rinds of functioning tissue that obscured central hemorrhagic degeneration. The second episode of hyperthyroidism might have occurred because of increased secretory activity of the persistent autonomous tissue, or perhaps even a second episode of hemorrhagic infarction. The data are not clear enough to determine which process was operative. The apparent remission of the second episode of hyperthyroidism after only four months of treatment with propylthiouracil is unusual for a toxic lesion, and suggests one of the causes of temporary toxicity described above.

If treatment of an autonomously functioning thyroid adenoma is necessary, it should be surgery or radioactive iodine therapy. Antithyroid drugs can control the toxicity, but they do not lead to an elimination of the lesion. Surgery is simpler for these patients and for those with Graves' disease because only the nodule need be removed. Experienced surgeons may be able to do this using regional block anesthesia, so as to minimize surgical risk. Preparation for surgery may be unnecessary if the patient is only pretoxic or has mild hyperthyroidism. Otherwise, a few weeks' treatment with antithyroid drugs is needed. One should avoid administering strong iodine solution because it is unnecessary and may cause the hyperthyroidism to flare.[9] Surgery may be preferred for most younger patients. Toxicity is more common in older patients, and often expresses itself in terms of cardiac decompensation, especially atrial fibrillation or congestive heart failure. For these patients radioactive iodine therapy is preferred. Occasionally preparation with antithyroid drugs is useful, while control of the cardiac status is being achieved. When radioactive iodine therapy is employed, a dose designed to ablate function of the autonomously functioning thyroid adenoma is best, otherwise there may be recurrent toxicity. To achieve ablation, 10 to 15 mCi of ^{131}I administered to the nodule is usually effective.

JOEL I. HAMBURGER, MD
4400 Prudential Town Center
Suite 275
Southfield, MI 48075

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Pulmonary arteriovenous malformations

Pulmonary arteriovenous malformations are vascular structures in the lung that allow blood to pass unoxygenated from the venous to the arterial circulatory system. They may occur in the form of a solitary lesion not associated with congenital anomalies or, more commonly, as multiple lesions that manifest the signs and symptoms of hereditary hemorrhagic telangiectasia. These rare disorders are usually discovered in the course of an examination to determine the cause of unexplained dyspnea, clubbing, polycythemia, hemoptysis, cyanosis, or gastrointestinal bleeding. The chest roentgenogram exhibits abnormalities in more than 90% of affected individuals.[1] Subsequent evaluation includes measuring arterial blood gas levels with the patient in the supine and upright positions, a computed tomographic scan with contrast media, and a pulmonary arteriogram to define the precise malformation. Documentation of the malformations is followed by resection, as in the case report by Kim et al[2] in this issue of the *Journal.*

These seemingly unimportant aberrations provide a unique opportunity to understand the normal physiologic functions of the lung. Indirect measurements of blood flow in the lung suggest that the flow is dependent on gravity, with more blood going to the bases of the lung when a patient is sitting or standing. Pulmonary arteriovenous malformations in the bases of the lung confirm this observation by showing that the shunting of blood increases in the upright position and may lead to severe hypoxemia when standing. This leads to the uncommon complaint of dyspnea upon standing up, known as platypnea. Getting out of bed in the morning becomes the equivalent of climbing to high altitude in the severely affected individual. In analogous fashion to the mountain climber, these patients hyperventilate at rest, complain of dyspnea on exertion at relatively low levels of exercise, and have an exaggerated ventilatory response to exercise.[3]

It has been suggested that resistance to flow through the normal pulmonary circuit increases at higher lung volumes. Studies in patients with malformations show an increase in shunting upon taking a deep breath, indicating that the blood preferentially flows through the malformations—the route with less resistance.[4] This may be due to a combination of increased resistance in the normal vascular route and decreased resistance to flow through the malformations due to the elastic recoil of the lung pulling on these abnormal vessels. This may worsen the hypoxemia experienced on exercising because the patients tend to breathe more deeply with exertion.

Because these patients become intermittently hypoxemic on standing up, they provide a unique opportunity to study the effects of periodic hypoxemia on the pulmonary blood vessels and on erythropoesis. It appears that some patients with malformations have pulmonary hypertension in spite of the low resistance to flow through the malformations themselves, suggesting that the mixed venous oxygen content may affect pulmonary vascular resistance.[5]

Pulmonary arteriovenous malformations are much more common in women.[6] The explanation for this is unknown, but it is of interest that primary pulmonary hypertension is more common in women. Furthermore, several reports suggest that bleeding from these malformations is more common during pregnancy and when a women is taking oral contraceptives.[7,8] Whether this is due to a direct effect on the vessels or an indirect effect through increased intravascular blood volume is unknown.

These malformations highlight a rarely mentioned function of the lung, that of acting as a carrier to the movement of bacteria from venous to arterial blood. It has been noted that cerebral abscesses occur most commonly in individuals with pulmonary arteriovenous malformations.[9] Presumably, the malformations provide a conduit for blood to flow directly to the arterial system from the oral cavity or gastrointestinal tract, or both. This conclusion is based on the observation that most of the organisms cultured from these abscesses are anaerobic or obligate anaerobes.

Treatment of these lesions has traditionally included surgery. The presence of multiple bilateral lesions precludes surgery and heretofore meant death due to complications from severe hypoxemia, or paradoxical embolization. Enter the new specialty of interventional radiology. Using balloons and other materials the radiologist can now obstruct these lesions, forcing blood to flow through the normal lung, with a dramatic increase in the arterial oxygen content. The value of this technique remains to be confirmed but appears to be promising.[3]

PETER B. TERRY, MD
Associate Professor
Respiratory Division
Department of Medicine
The Johns Hopkins University
School of Medicine
Baltimore, MD 21205

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Paradoxes related to the management of missile wounds of the thorax

The chances of survival following an M-16 rifle wound in the United States are less than those associated with a similar wound incurred in Vietnam in 1964. This paradox relates to three facts: (1) the round fired from the M-16, or its equivalent in the United States, is probably a hollow-nosed, soft-pointed bullet, as opposed to the one fired from the same weapon in Vietnam—a copper jacketed bullet (mandated by the Hague Convention, 1906, for humanitarian reasons); (2) rapidity with which the wounded were transferred from the site of injury to a major treatment facility favored Vietnam; and (3) in general, expertise of wound care was greater in Vietnam. This paradox implies that education in ballistics and gunshot wounds is necessary during peace time in this country, if loss of life and limb is to be minimized. Despite the enormity of trauma that can be caused by motor vehicles and guns in the United States, the American College of Surgeons' Committee on Trauma estimated that only 25% of the examinees for the first part of the American Board of Surgery's qualifying examination were experienced in the management of victims of trauma. This is an additional paradox, one which reemphasizes the need for education in the management of gunshot wounds.

Obviously, effective gun control would be an alternative to additional training of trauma teams, but for the moment that seems unlikely.

Guns have exceeded pointed instruments as weapons of assault in the United States.[1,2] Twenty-three thousand Americans die annually from injuries sustained by handguns.[3] The chest is a common target. Among United States troops in the Korean and Vietnam wars, nearly 40% of fatal wounds were wounds of the thorax.[4,5] There were 4 times as many fatalities from thoracic wounds as from abdominal wounds,[4,5] despite the "protection" of the thoracic viscera by a bony cage and, in the Vietnam war, by a protective garment shielding mainly the thorax. The difference is accounted for in part by the relatively greater exposure of the upper parts of the body to high velocity missiles, and the presence in the thorax of the more immediately necessary organs that serve circulation and respiration. In part, however, this difference can be attributed to the greater likelihood of secondary missiles of bone from the thoracic cage and of metal from protective garments.

The energy a missile imparts to tissue determines the degree and extent of tissue damage. The greater the density of the tissue and the greater the profile area of the missile perpendicular to its track, the greater is the rate at which the missile transfers its energy to tissue and surrounding garments. This transfer of energy is often so great in the instance of bone and metal, that osseous and metallic fragments become destructive secondary missiles, tracking in directions different from the primary missile.

In treating missile wounds it is generally advisable to radiograph not only the injured region, but also one region above and below the injured area. This rule is particularly applicable in missile wounds of the thorax, in which secondary missiles with unpredictable and destructive tracks are more likely to be encountered. In chest wounds, posteroanterior and lateral radiograms of the neck and abdomen are indicated. The thorax, despite the fact that it contains such an array of immediately necessary structures, is the only region of the body where surgical exploration is not routine following penetrating injuries. No more than 15% of such wounds require thoracotomy.[6-10] The others respond to tube thoracostomy alone. In contrast, a penetrating missile wound of the abdomen or neck virtually always demands surgical exploration.[11] The indication for tube thoracostomy following a missile wound of the thorax is primarily the finding of diminished breath sounds on auscultation, indicative in such cases of hemothorax, pneumothorax, or hemopneumothorax. Radiographic confirmation of this interpretation need not precede tube thoracostomy. However, if vital signs are normal and stable and radiographic documentation is desired, the patient should be accompanied by a physician through radiography, since cardiopulmonary function can deteriorate rapidly in such cases. Posteroanterior and lateral radiograms in the erect position are preferable, but often patients with missile wounds will not tolerate this position. Radiography in the supine position is not an acceptable alternative, since it may fail to reveal a large volume of fluid in a pleural cavity. A preferable alternative is the lateral decubitus position, with the injured side dependent. In fact, this is the radiographic view of choice for the detection of small volumes of fluid in a pleural cavity.

The indications for tube thoracostomy in patients with missile penetration of the thoracic wall include decreased breath sounds; radiographic evidence of intrapleural fluid in sufficient volumes to impair respiration, and demonstration upon laparotomy of penetration of the respiratory diaphragm. Thoracentesis has largely lost its utility in the management of missile wounds of the chest. Tube thoracostomy can be accomplished with sufficient rapidity for diagnosis and with greater effectiveness than thoracentesis. There should be little hesitation in using it in trauma centers.

In patients with missile wounds of the thorax and blood draining from a thoracostomy tube, correct pathophysiologic interpretation of the color of the blood is useful. Usually such blood is dark red, and hence poorly oxygenated. Its source may be a laceration of pulmonary parenchyma where oxygenation is impaired by partial retraction of the lung, a pulmonary vein draining a poorly ventilated lung, or more commonly, because of its higher blood pressure, a pulmonary artery or its branches. The blood draining from a thoracostomy tube may be bright red; this should alert the physician to the probability of injury to a systemic artery such as an intercostal, internal thoracic, or subclavian artery, or the aorta or left side of the heart. An immediate thoracotomy is required to control hemorrhage.

Sometimes, blood hemorrhaging into the pleural cavity from a lacerated pulmonary arterial branch or pulmonary parenchyma drains through a thoracostomy tube as bright red blood.[12] How is this blood oxygenated? Full oxygenation of extravasated intrapleural blood can be accomplished by respiratory pleural movement if a pneumohemothorax exists. Since air recently introduced into a pleural cavity contains oxygen at a partial pressure greater than that of alveolar air, and since the movement of visceral and parietal pleural surfaces with respiration readily affects equilibration of intrapleural blood with intrapleural air, a pneumohemothorax is an alternative cause of bright red drainage through a thoracostomy tube. Since the partial pressure of oxygen in a blood sample can be easily measured in a well-equipped trauma center, the distinction between systemic arterial, left atrial, or ventricular bleeding into a pleural space from intrapleural hyperoxygenation of pleural blood in a pneumohemothorax can be determined. Thoracotomy is reserved for arterial or ventricular bleeding.

Intrapleural bleeding or accumulation of air from a lacerated lung is likely to continue if the lung remains contracted in a hemothorax, pneumothorax or pneumohemothorax, yet usually stops promptly with evacuation of pleural fluid and full reexpansion of the lung. Faced with this situation, one might expect that stretching the lung and its visceral pleura might facilitate the bleeding or leakage of air. The mechanism of this apparent sealing is not understood, but the urgency of prompt reexpansion is well recognized by those experienced in managing trauma to the chest. There are two other reasons for prompt evacuation of pleural blood in acute care of thoracic missile wounds: first, since a pleural cavity can contain as much as three liters of blood with retraction of a lung and mediastinal shift, impairment of ventilation can develop rapidly and be fatal; second, intrapleural blood in acute cases is partially defibrinated by pleural movement and is eminently suitable for autotransfusion.[11]

Finally, blunt trauma may prove more threatening than penetrating trauma. Blunt trauma, without fracture of the bony thoracic cage or flail chest, can be induced by missiles glancing off the thoracic wall, direct impact over a large surface by a large object, a small missile at very high velocity,[11] or the near equivalent of blunt trauma, a shotgun blast at close range.

Injury from blunt trauma is generally less evident and more likely to be overlooked. For blunt trauma to be recognized and documented there must be significant dysfunction and damage. A third reason for blunt trauma to prove more dangerous than penetrating trauma lies in the edematous thickening of the blood-gas barrier in pulmonary inflammation following trauma.[12] The blood-gas barrier is virtually limited to that region of the alveolus where the pulmonary epithelium is separated from the capillary endothelium by no more than a single basal lamina.[13] The diffusion rates of metabolic gases between alveoli and pulmonary capillary blood are proportional to the thickness of this blood-gas barrier and its area. In blunt trauma, the extent of edematous thickening of the blood-gas barrier is likely to be much greater than in penetrating trauma, and even though the local thickening of the blood-gas barrier in the region of the injuried pulmonary parenchyma may be less than in penetrating trauma, the overall effect may be to so reduce diffusion capacity that intractable hypoxemia necessitates surgical resection of the injured parenchyma.[14]

Recognition of the paradoxes that relate to missile wounds of the thorax and an understanding of the methods used to resolve these paradoxes may serve as guides in treating wounds that demand prompt decision and action.

KENNETH G. SWAN, MD
JOYCE M. ROCKO, MD
Department of Surgery
University of Medicine and Dentistry
of New Jersey
New Jersey Medical School
Newark, NJ 07103

1. Rohman M, Ivatury RR, Steichen FM, et al: Emergency room thoracotomy for penetrating cardiac injuries. *J Trauma* 1983; 23:570–576.
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Portions of this report were based on a presentation at the New York Society for Thoracic Surgery on November 13, 1980.

Treatment of ovarian vein thrombosis

The report of Adachi, Segen, and Li in this issue of the *Journal* describing a patient with ovarian vein thrombosis illustrates the difficulties in diagnosing this disorder. Patients with ovarian vein thrombosis often have confusing and even contradictory symptoms and signs that require careful evaluation.

Because ovarian vein thrombosis is easily confused with ectopic pregnancy, it is critical to determine whether or not a patient is pregnant. A beta-human chorionic gonadotropin (beta-HCG) level of less than 4 mU/mL rules out gestation. However, in institutions in which this test is not readily available, pelvic pain of recent onset, amenorrhea, and an adnexal mass would be suggestive of ectopic pregnancy, until this alternative can be ruled out with absolute certainty.

Quantitative serial beta-HCG levels can be used to evaluate a viable intrauterine pregnancy. If the beta-HCG level during the early weeks of pregnancy does not double every two and a half to three days, ectopic pregnancy or impending abortion is strongly suggested. During this interval, ultrasound of the pelvis should be performed to evaluate the uterine cavity. This study can help evaluate the uterine adnexa and confirm the presence of an intrauterine contraceptive device. The combination of ultrasound and beta-HCG analysis provides greater reliability than either study alone. The use of culdocentesis to detect hemoperitoneum has declined due to the increased use of laparoscopy; this technique was not used by Adachi et al.

Examination under anesthesia does not often provide any new information. The risk of anesthesia is sufficiently great as to warrant a detailed discussion of all possible surgical outcomes and an understanding of the patient's wishes and those of her family prior to the procedure. Informed consent must be obtained, and any surgery should be tailored as much as possible to the patient's desires concerning future childbirth. In the absence of a surgical emergency, an elective appendectomy at the time of laparotomy should be considered.

In the case described by Adachi and colleagues the findings at surgery suggested previous spontaneous abortion or tubal abortion with resorption. In the absence of detectable pulmonary emboli or septic pelvic thrombophlebitis, it is unlikely that this patient would be given anticoagulant therapy or that an evaluation for deep vein thrombosis would be instituted. The minidose heparin employed may have aided in this patient's recovery, and indeed, may be of great benefit in selected patients undergoing any pelvic procedure.

The proof for effective management of ovarian vein thrombosis is the long term recovery of the patient. Each case should be managed on an individual basis, with each episode in a particular patient evaluated as an independent event. Treatment should be based on a keen awareness of other possible disorders, particularly life-threatening ones such as ectopic pregnancy.

MICHAEL B. COHEN, MD
Department of Obstetrics and Gynecology
Tulane University Medical Center
New Orleans, LA 70112

Address correspondence to Editor, New York State Journal of Medicine, *420 Lakeville Road, Lake Success, NY 11042. Letters should be typed double-spaced and include the signature, academic degree, professional affiliation, and address of each author. Preference is given to letters not exceeding 450 words, and every effort will be made to assure prompt publication. All letters are personally acknowledged by the Editor.*

Gunshot wound of the brachiocephalic artery with peripheral bullet embolization

TO THE EDITOR: Reports of survivors from gunshot wounds to the brachiocephalic artery are being seen with increasing frequency in the literature. In this report we note that a bullet that resided in the brachiocephalic artery was not located during brachiocephalic exploration. After surgery the bullet was found to be occluding the right brachial artery.

Case Report. A 24-year-old man arrived in the emergency room of St. Joseph's Hospital after sustaining a wound from a 9 mm handgun to the left sternoclavicular junction.

The patient was alert, and was able to speak and to move all four extremities. His blood pressure was 110/70 mm Hg in both arms; pulse rate, 95 beats/min; respiratory rate, 20/min. There was minimal swelling at the base of the neck and in the suprasternal region. The chest was clear to bilateral percussion and auscultation. Carotid, radial, and femoral pulses were present and symmetric.

Bilateral lower extremity venous access was obtained and a right radial arterial line was inserted A chest roentgenogram demonstrated a widened superior mediastinum with deviation of the trachea to the right. There was a foreign, metallic body on the left clavicular head, with the bullet resting beneath the right sternoclavicular junction. Fluoroscopy showed pulsatile motion of the projectile. Angiograms in the anteroposterior and left anterior oblique positions demonstrated a bullet lying in a transverse position in the distal part of the brachiocephalic artery near the bifurcation. There was a small pseudoaneurysm on the superior aspect of the brachiocephalic artery, 0.5 cm proximal to the bullet. About three quarters of the bullet was lying inside the artery and one quarter outside the artery. Both common carotid arteries originate from the brachiocephalic artery (Fig 1).

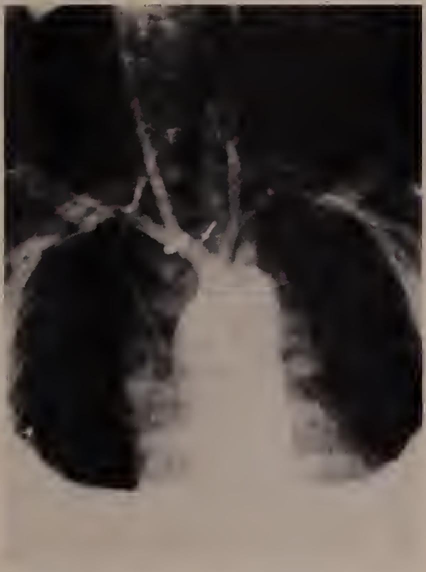

FIGURE 1. Anteroposterior angiogram shows anomalous origin of left common carotid artery, 1-cm pseudoaneurysm (arrow), and bullet partially exiting distal brachiocephalic artery.

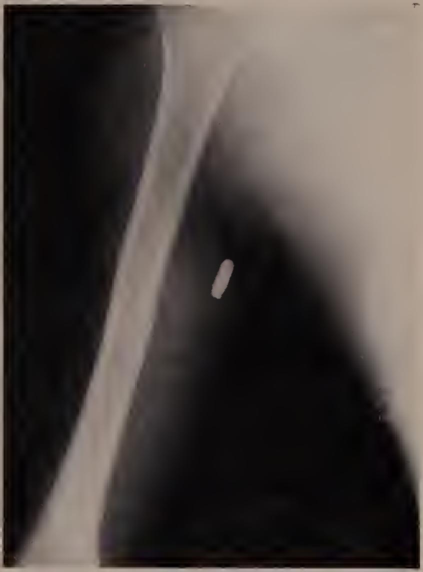

FIGURE 2. Postoperative roentgenogram of right arm shows bullet lodged in brachial artery.

An upper median sternotomy and right anterior thoracotomy with supraclavicular extension were performed. It was possible to obtain control of the brachiocephalic artery just distal to the left common carotid artery. The proximal right subclavian and right common carotid arteries were also controlled. Lateral arteriorrhaphy was used to close both entrance and exit wounds. A thorough search for the bullet was unsuccessful. In the recovery room the right radial arterial line suddenly ceased to produce a tracing, as the right arm was cool and without a pulse. A chest film did not show a bullet in the chest. A roentgenogram of the right arm located the bullet in the right brachial artery (Fig 2). It was removed under local anesthesia with restoration of flow to the hand. The patient did well after surgery and was discharged seven days later.

Discussion. Experience with brachiocephalic arterial injury has been derived primarily from civilian series. DeBakey,[1] Hughes,[2] and Makins[3] found no reports of brachiocephalic arterial injury in World War I, World War II, or the Korean conflict. Rich et al[4] reported three brachiocephalic arterial injuries from the Vietnam Vascular Registry, which accounted for 0.3% of the total arterial injuries.

In civilian series there were 10 cases reported between 1960 and 1978.[5]

In 1982 Graham et al[6] reported 45 brachiocephalic vascular injuries. There have been only sporadic reports of arterial bullet embolization from gunshot wounds to the great vessels.[7,8]

This case probably represents bullet embolization secondary to operative manipulation of the great vessels in an attempt to achieve vascular control. The bullet traveled to its final position of occlusion while moving the patient from the operating room to the recovery room.

ROBERT J. WARD, MD
Department of Surgery
North Shore University Hospital
Manhasset, NY 11030

THOMAS F. NEALON, JR, MD
Department of Surgery
St. Vincent's Hospital and Medical Center
New York, NY 10021

DAVID BREGMAN, MD
Department of Surgery
St. Joseph's Hospital and Medical Center
703 Main St.
Paterson, NJ 07503

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See also p 540–542.

Elevated carcinoembryonic antigen in tuberculous pericarditis

TO THE EDITOR: It is well known that carcinoembryonic antigen (CEA) levels can be used as a marker for colorectal, pancreatic, and pulmonary malignancies.[1] Elevated levels can also be found in nonmalignant conditions such as inflammatory bowel disease, alcoholic cirrhosis, tuberculosis, pancreatitis, emphysema, and benign neoplasms.[1,2] Levels greater than 20 ng/ml are often associated with colorectal carcinoma that has metastasized to hepatic or osseous tissues.[3,4] This report describes a patient with tuberculous pericarditis and an extremely elevated CEA level (178 ng/ml). Extensive studies failed to reveal associated malignancy.

Case Report. A 73-year-old man was admitted to the Buffalo General Hospital for treatment of hypertension, arteriosclerotic heart disease, and alcohol abuse. Three weeks prior to admission he noticed the gradual onset of malaise, poor appetite, and weakness. He had lost 11 pounds in four months.

Physical examination revealed a thin man with apparent chronic illness. His temperature was 103°F; respiratory rate, 28/min; heart rate, 120/min; blood pressure, 95/70 mm Hg. Pulsus paradoxus was 15 mm Hg.

Examination of the head, ears, eyes, nose, and throat was unremarkable. There were no jugular venous pulsations, and Kussmaul's pulses were absent. The chest sounds were clear. The point of maximal impulse was displaced laterally, and the heart sounds were distant. There was no heart murmur or cardiac rub. On abdominal examination the liver was normal and there was no splenomegaly. There was no costovertebral tenderness. The prostate was not enlarged, and analysis of the stool was negative for heme. There was no lymphadenopathy.

The white blood cell count was 6,800/mL[3] with 47% neutrophils, 16% band forms, 20% lymphocytes, 2% eosinophils, and 15% monocytes. Laboratory studies were within normal limits for electrolytes, glucose, creatinine, and blood urea nitrogen. Liver function test results were serum glutamic oxaloacetic transaminase, 117 U/mL; serum glutamic pyruvic transaminase, 74 U/mL; lactate dehydrogenase, 287 U/mL; and total bilirubin, 0.9 mg/dL.

An electrocardiogram exhibited areas of low voltage and evidence of an inferior wall myocardial infarction. A chest roentgenogram had a markedly enlarged cardiac silhouette with no pulmonary infiltrates or pleural effusion. An echocardiogram showed a large pericardial effusion.

The patient had daily temperature spikes to 102° to 104°F. Cultures of blood and urine were negative. Sputum samples had 1+ white blood cells and grew normal flora. Multiple sputum smears were negative for acid-fast bacilli, and the patient had diminished reactivity to 5 tuberculin units of purified protein derivative, 250 tuberculin units of purified protein derivative, mumps, and Candida skin tests. Assays for antinuclear antibodies and antibodies to lupus erythematosus were negative. Thyroid function studies were within normal limits, and a hepatitis screen was consistent with a previous infection with hepatitis B virus. A slide flocculation test for syphilis was negative. Cytomegalovirus and Epstein-Barr virus titers were consistent with past or recent infections. The alpha-fetoprotein level was within normal limits. The CEA level was 178 ng/mL (normal, less than 5.0 ng/mL).

A pericardiotomy was performed, which revealed a pericardial fibrinous exudate yielding a typical "bread and butter" appearance.[5] One thousand milliliters of straw-colored fluid was removed, which contained 325 white blood cells/mL[3] (36% neutrophils, 56% lymphocytes, and 8% macrophages) and 243 red blood cells/mL[3]. The level of glucose was 41 mg/dL; protein, 4.9 g/dL; and lactate dehydrogenase, 1,631 U/mL. Routine bacterial fungal cultures were negative.

An occasional acid-fast bacillus was seen on microscopic examination of the pericardial biopsy. *Mycobacterium tuberculosis* was cultured from the biopsy specimen and the pericardial fluid.

Results of a barium enema, an upper gastrointestinal roentgenographic series, and a computerized tomographic scan of the abdomen were unremarkable.

The patient was begun on therapy with oral isoniazid, 300 mg daily; oral rifampin, 600 mg daily; and oral prednisone, 80 mg daily. Reports of cultures identified *Mycobacterium tuberculosis* that was sensitive to these medications. Dramatic clinical improvement was seen, and a follow-up CEA level after six weeks of therapy was 2.9 ng/mL.

Discussion. Elevated CEA levels can be seen in patients with tuberculosis, but none of 30 patients reported by Hansen et al[1] had a level greater than 10 ng/mL. A search of the medical literature has not revealed a case of tuberculosis with such an extreme elevation in CEA. This case shows that markedly elevated CEA levels can also be found in tuberculosis pericarditis without associated malignancy.

JAMES DESEMONE, MD
DONALD A. OPILA, MD
Department of Medicine
The Buffalo General Hospital
100 High St
Buffalo, NY 14203

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Fatal strongyloidiasis in immunosuppressed patients

TO THE EDITOR: The articles by Dellacona et al[1] and Kimmelstiel and Lange[2] as well as the accompanying editorial[3] indicate that serious, even fatal, infection with *Strongyloides stercoralis* is not as uncommon in the United States as one might previously have thought. I and two co-authors[4] reported on four patients who developed significant *S stercoralis* infection. Two patients had malignant lymphoma, and two had received prolonged prednisone therapy for bullous pemphigoid and for idiopathic thrombocytopenic purpura. This potentially fatal infection should be considered in all patients receiving immunosuppressive or cytotoxic therapy for underlying disorders.

FRED ROSNER, MD
Queens Hospital Center Affiliation of the
Long Island Jewish-Hillside Medical Center
Jamaica, NY 11432

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The value of echocardiography in left atrial myxoma in a child

TO THE EDITOR: Primary tumors of the heart and the pericardium are rare, with an incidence between 0.001 and 0.28% in reported autopsy series. Myxomas are the most common form of cardiac tumor (13.5%) when all age groups are considered.[1] Our purpose is to discuss the value of echocardiography in diagnosing intracardiac tumors.

Case report. A 14-year-old girl was admitted to the hospital complaining of a cough and breathing difficulties for seven days, and abdominal pain for three days. Two weeks prior to admission she had fever for two days. When the fever subsided she noticed that her cheeks and eyelids were puffy, and that she could not sleep comfortably without two pillows.

On admission, her heart rate was 120/min; respiratory rate, 46/min; blood pressure, 110/80 mm Hg; and temperature, 37°C. Bilateral engorged external jugular veins and periorbital and pretibial edema were noted. The lungs were clear to auscultation. The liver was firm and tender, extending to the right lower quadrant. Cardiac examination revealed that the point of maximal impulse was at the sixth left intercostal space outside the mid-clavicular line. The precordium was hyperactive with a parasternal heave. The heart rhythm was regular. The first heart sound was normal, and the second heart sound was loud and single. A grade II/VI ejection systolic murmur and a "gallop" sound were heard at the apex. A pericardial rub was noted at the apex with the patient in the supine position; however, it disappeared when the patient was in the sitting position. The most useful diagnostic test was an echocardiogram (Fig 1).

The patient underwent open heart surgery. A large ($4\frac{1}{4} \times 3\frac{1}{2}$ cm) pedunculated, pale, yellow gelatinous tumor mass was removed from the left atrial cavity, along with a small piece of the interatrial tissue to which the tumor was attached. On pathologic examination the tumor was identified as a myxoma. Her postoperative course was unremarkable.

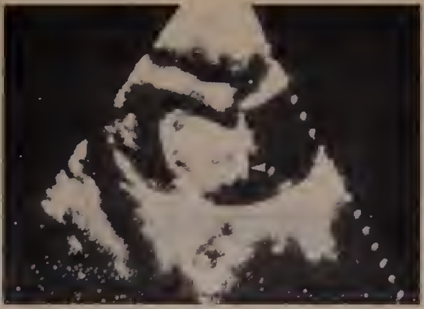
FIGURE 1. Two-dimensional echocardiogram during systole showing a pedunculated mass of echos (arrow) obliterating the mitral valve leaflets. Note that there is pericardial effusion behind the posterior wall of the left ventricle.

Discussion. Seventy-five percent of all cardiac myxomas occur in the left atrium; the majority of the remaining tumors are found in the right atrium. Multiple myxomas in a single patient have been described by McAllister.[1] The major symptoms of myxomas are due either to fragmentation of the tumor, causing embolism, or a mass occupying the cavity that causes obstruction of blood flow. This patient had rapid onset of congestive heart failure. We believe this was secondary to hemorrhage within the tumor mass that caused rapid enlargement of the mass and obstruction of the mitral valve. A biopsy showed evidence of hemorrhage in the tumor. The chest film and electrocardiogram were not specific for a diagnosis of myxoma. An echocardiogram is very sensitive in detecting intracardiac myxoma. Both an M-mode and 2-D echocardiogram can detect an intracardiac tumor; however, a 2-D echocardiogram can better delineate the mass—its size, location, attachment, and motion with the cardiac cycle. An M-mode echocardiogram may not be able to depict a right atrial mass. With a 2-D echocardiogram other associated anomalies can be ruled out. A thorough echocardiographic study should be performed before subjecting a patient to open heart surgery without cardiac catheterization and cineangiocardiography.

McGarry et al[2] reported false negative diagnoses in 3 of 13 (23%) patients treated with catheterization and 2 of 10 (20%) patients treated with angiocardiography; however, echocardiography was positive in 5 of 5 (100%) patients. Cardiac catheterization—especially transseptal cardiac catheterization—may dislodge the tumor and cause embolism.[3] A false positive diagnosis of atrial myxoma by echocardiography is possible when an excessive instrument gain setting is used.[4] Myxoma can be missed if the sensitivity of the instrument is so low that the ultrasound energy is insufficient to penetrate the anterior mitral leaflets. An echocardiogram of the left atrial myxoma may sometimes be confused with mitral stenosis, left atrial thrombus, or a large vegetation of the mitral valve; however, with 2-D echocardiography these can be differentiated. Complete surgical excision of the tumor, with excision of a small portion of the interatrial septum (where the base is attached), should be performed to prevent a recurrence.

The prognosis for patients with atrial myxoma is excellent. Periodic echocardiographic examination should be performed to detect recurrences. Echocardiography is extremely helpful in diagnosing intracardiac tumors, and it can replace cardiac catheterization in a weak patient.

BROJENDRA N. AGARWALA, MD
MANOJ SHAH, MD
Department of Pediatrics
Mount Sinai Hospital Medical Center
Chicago, IL 60608

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Flexible fiberoptic bronchoscopy in the elderly

ROBERT D. BRANDSTETTER, MD, SALVATORE A. CROCE, MD, ELLEN SCHIAFFINO, MD, RUEBEN OTERO, MD, FRANK E. IAQUINTA, MD

ABSTRACT: The safety of fiberoptic bronchoscopy was studied in a group of 100 hospital patients 65 years of age or older who underwent bronchoscopy on 180 occasions. Premedication and the local administration of lidocaine were well tolerated. Inspection and lavage resulted in the least morbidity. Of the 180 procedures, tachy- or brady-arrhythmias were observed in 4.4% and postoperative fever in 5.5%. The most significant finding was the high incidence of bleeding, which occurred in 18 of 88 biopsies, an incidence of 20.5%. One death was due to major hemorrhage following transbronchial biopsy while the patient was given mechanical ventilation. Continuous oxygen therapy and electrocardiographic monitoring are recommended during the procedure and, in selected cases, during the postoperative period.

(NY State J Med 1984; 84:546–548)

INTRODUCTION

Although flexible fiberoptic bronchoscopy is performed in an increasing number of elderly patients, there are no reports that assess the safety of bronchofiberoscopy in this particular group of patients. This report describes a prospective study to evaluate the safety and diagnostic or therapeutic results of bronchoscopy in a patient population of 65 years of age or older.

PATIENTS AND METHODS

A prospective study of patients 65 years of age or older was performed from July 1, 1982 to January 14, 1984 to evaluate the safety of bronchoscopy. All patients had multiple medical illnesses and were receiving several medications which were not discontinued or adjusted for bronchoscopy. Three hundred and thirty-two patients in this age group with pulmonary disorders were evaluated, with 100 non-consecutive patients having 180 bronchoscopic procedures. Of the 100 patients that required bronchoscopy, 59 (59%) were men and 41 (41%) were women. The patients ranged in age between 65 and 101 years (mean, 77.3 years): 44 patients (44%) were between 65 and 75 years; 43 patients (43%) were between 76 and 84 years; and 13 patients (13%) were 85 years of age or older. Informed consent was obtained from all patients. Minimum preoperative laboratory determinations included a chest roentgenogram, electrocardiogram, complete blood count, platelet count, prothrombin time, partial thromboplastin time, electrolyte levels, and blood urea nitrogen. The only patients who had continuous electrical monitoring of cardiac rhythm were those on ventilators (71 bronchoscopic procedures). Otherwise, patients had a nurse in attendance who continuously took a manual, brachial artery pulse.

Bronchoscopic procedures were performed with the Olympus BR-4B2 bronchoscope. Three L/min of nasal cannula oxygen was administered to all patients 20 minutes before bronchoscopy if the transnasal route was used, and 100% O_2 was given via either ventilator or wall unit delivery if the endotracheal or transtracheal route was used. Special side port adaptors (Portex, Inc swivel adaptor),[1] allowed insertion of the bronchoscope without disconnecting the patient from the respirator. Oxygen was administered throughout and up to two hours after the procedure, with all patients having their supplemental O_2 level maintained before bronchoscopy readministered two hours after the procedure. A chest roentgenogram was taken of each patient four and 24 hours after bronchoscopy. Bronchoscopy was performed at bedside on 73 patients; another 27 patients had transbronchial biopsies performed in radiology under fluoroscopic control. One patient, however, underwent a transbronchial biopsy in the intensive care unit because she could not be transported.

Patients who underwent transnasal bronchoscopy received intramuscular injections of phenergan, 25 mg, demerol, 25 mg, and atropine, 0.6 mg, one half hour before the procedure. Patients who had an endotracheal tube or tracheostomy tube in place received only 0.6 mg of intramuscular atropine. On five occasions, atropine was not administered because of tachycardia. If the transnasal route was used, the most patent naris was anesthetized with 2% viscous xylocaine jelly. The posterior oropharynx and vocal cords were anesthetized with a spray atomizer device using 4% xylocaine to minimize cough and bronchospasm during the procedure. The total dose of xylocaine preparations ranged from 110 mg to 210 mg. Inspection of the tracheobronchial tree involved an attempt to visualize the vocal cords, trachea, and all major bronchi.

Bronchial lavage of the tracheobronchial tree and its segments was performed using 3 to 100 cc of sterile isotonic saline according to the procedure (atelectasis, mucous plugging). In one patient, bronchial lavage included the administration of 20 cc of 10% acetyl cysteine, with isoetharine to avoid bronchospasm, on five occasions for liquification of inspissated secretions. The combination of inspection and lavage excluded any biopsy forceps procedure.

Bronchial brushings were performed using the Medi-tech brush (BRW/1.0/70/90). All bleeding was quantified during bronchial brushing by collection in a sterile Specimen Trap (CP5-7240). Endobronchial biopsy was performed using an Olympus forceps (FB-19C). At least two to four biopsies were taken of each visible lesion.[2] Quantification of bleeding was once again assessed, with cautious use of epinephrine solution (1:

From the Departments of Medicine, New Rochelle Hospital Medical Center, New York Medical College (Drs Brandstetter, Schiaffino, Otero, and Iaquinta); and Pulmonary Diseases (Dr Croce), University of Medicine and Dentistry of New Jersey-Rutgers Medical School.

Address correspondence to Dr Brandstetter, Assistant Director, Department of Medicine, New Rochelle Hospital Medical Center, 16 Guion Place, New Rochelle, NY 10802.

TABLE I. Complications Related to Procedures

	Inspection and Lavage	Bronchial Brushing	Endobronchial Biopsy	Transbronchial Biopsy	Total
Number of procedures	92	40	20	28	180
Minor hemoptysis, >20 cc and <50 cc in 24 hr		7	3	6	16
Major hemoptysis, >50 cc in 24 hr			1		1
Fatal hemoptysis				1	1
Fever, ≥101°F in less than 8 hr after flexible fiberoptic bronchoscopy	5	2	2	1	10
Dysrhythmia, supraventricular tachycardia-bradycardia	2	4	1	1	8
Pneumonia, new infiltrate within 24 hr of flexible fiberoptic bronchoscopy	1				1
Laryngitis	1			1	2
Chronic cough, >12 hr after flexible fiberoptic bronchoscopy		1			1
Iatrogenic air fluid level	1				1
No. of complications (%)	10(11%)	14(35%)	7(35%)	10(36%)	41(23%)

10,000) to control bleeding.

Transbronchial biopsy was performed using the technique described by Zavala[3,4] in 14 of a series of 28 patients who had been biopsied. Bleeding was controlled in all but one patient and was quantitated in the same fashion as described for bronchial brushings and endobronchial biopsy. At least two to six biopsy specimens were obtained[4] except in the one patient with fatal hemoptysis.

RESULTS

The most common reasons for requesting bronchoscopy were retained secretions (37%) and infiltrates (36%). The left lower lobe was the region of retained secretions nearly twice as often as the right lower lobe (42 versus 25 episodes). Tumor masses comprised 8% of the indications for bronchoscopy, with an additional 6% for hemoptysis.

Bronchoscopy was performed via the transnasal route 58% of the time, primarily for diagnostic purposes. The endotracheal and transtracheal routes were used equally for diagnostic (17 versus 20 procedures) and therapeutic (13 versus 14 procedures) measures, respectively. In general, as many bronchoscopic procedures were performed as were inspection and lavage procedures: 88 versus 92.

Table I lists the complications related to bronchoscopy according to type of procedure. Forty-one bronchoscopic complications were recorded. Hemoptysis following 88 procedures was the most frequent complication (20.5% of biopsies), with 16 minor, one major, and one fatal event. Fever and dysrhythmias complicated inspection and lavage and bronchoscopic procedures, with 10 episodes of fever (5.5%) and eight documented alterations in heart rhythm (4.4%).

DISCUSSION

The results of this study demonstrate a range of applications of the flexible fiberoptic bronchoscope and an acceptable level of safety. Bronchoscopy was performed most often for diagnostic purposes, and the transnasal route was employed most frequently, without an immediate adverse effect. The endotracheal and transtracheal routes were used most often in patients with retained secretions and mucous plugging.

The number of procedures performed was distributed almost equally among inspection and lavage and various biopsy techniques. Most of the biopsy procedures, and all but one transbronchial biopsy, were limited to the patients who underwent bronchoscopy via the transnasal route. This finding was not surprising because the patients who required a biopsy procedure most often had an infiltrate or tumor mass. These patients did not have pre-existing artificial airways, which are associated with retained secretions or mucous plugging and often provoke the inspection and lavage procedure.

The indications for bronchoscopy in the elderly are not different from previous studies in the general population.[5] The exception, however, is that there is a tendency to perform bronchoscopy more often for infiltrates and retained secretions in elderly patients.[1] We found, as in Barrett's study,[1] that retained secretions were suspected when findings on chest roentgenograms suggested atelectasis, and inadequate suctioning was suspected when there were persistent adventitious sounds or elevated peak pressures on the ventilator. Physical therapy of the chest has been used in patients with non-life threatening retained secretions, but was often tolerated poorly by the elderly. Bronchoscopy would therefore be performed on a routine basis, with the understanding that the benefits accrued from removal of secretions are frequently transient, but may also save lives.

When one reviews the physiologic alterations that occur in the aging lung,[6] and combines these with altered mental status and immobility, impaired cough reflex, impaired swallowing ability that provokes chronic aspiration, and impaired host defense mechanisms, it is understandable why pulmonary infections and retained secretions are more common in the elderly.[7]

Other indications for bronchoscopy included three patients with pleural effusions,[8] as well as one patient with a history of smoking, fibrobullous disease, and a suspicious sputum cytology.

Forty-one complications were recorded, with two episodes of hemoptysis that were of significant concern. Two other complications encountered frequently were fever and dysrhythmias. The findings of hemoptysis, fever, and dysrhythmias complicating bronchoscopy have been the most widely reported.[9-11]

Hemoptysis (>50 cc) occurs as a complication of bronchoscopy most often in association with a biopsy procedure; the risk of hemoptysis is related to the level of experience of the bronchoscopist and the underlying clinical condition.[9,12] An increased risk of bleeding has been noted particularly with transbronchial biopsy, where special techniques to control bleeding have been suggested.[3,9,12] Prior to this study, groups at risk for increased bleeding have included patients with immunosuppression or uremia,[9] as well as those with altered coagulation states.[12] Most of the patients in this series who had bleeding of more than 20 cc had friable mucosa of the tracheobronchial tree. The one patient who had an endobronchial biopsy associated with major hemorrhage had a noticeably friable mucosa over the visible tumor. The one fatal case of hemoptysis following transbronchial biopsy was a woman with progressive infiltrates who was found to have an underlying malignancy and coagulopathy. These seriously ill patients and the altered integrity of the lung, however, may not fully explain the increased bleeding seen in this study.

Our initial technique of transbronchial biopsy increased the risk of bleeding: bleeding occurred in six of the first 14 biopsies, in which the wedge technique as described by Zavala[3] was not employed. The last 14 transbronchial biopsies in this series were done using this published technique, with only one bleeding episode.

The one death from hemoptysis following transbronchial biopsy occurred while the patient was being ventilated on a ventilator. Although transbronchial biopsy performed on a patient receiving ventilatory support is not generally recommended, we felt that the patient's deteriorating status and worsening infiltrates warranted the procedure. Indeed, this case demonstrates the high morbidity of transbronchial biopsy when performed under these conditions.

Ten episodes of transient fever (≥101°F), up to eight hours following bronchoscopy were observed in this study. They occurred with equal frequency among the inspection and lavage and biopsy procedures. Fever may be secondary to contamination of the lower respiratory tract with organisms dragged down by the bronchoscope, or due to areas of microatelectasis secondary to sloughed mucosa or minimal secretions.

The finding of only eight episodes (4.4%) of transient, self-limited tachy- or brady-dysrhythmias during bronchoscopy compares favorably with large studies in which dysrhythmias have ranged up to 80%.[13] The low occurrence of dysrhythmias may have been related to supplemental oxygen therapy that prevented the associated hypoxemia.[14] More likely, however, is that since we did not monitor most of the patients, subtle, minor dysrhythmias that would be recorded with continuous monitoring were missed.[10,15]

The other complications that we encountered during bronchoscopy included pneumonia, laryngitis, cough, and iatrogenic air fluid levels following lavage in a patient with fibrobullous disease. No patient had a pneumothorax. We attribute this success to the technique of withdrawing the forceps from contact with the pleura when the patient indicates pleuritic pain.[16] Another site would then be probed, and a biopsy taken only when no pain occurred with the forceps locked.

We have shown that the procedure of bronchoscopy introduced via any route can be performed safely in a hospital setting in patients 65 years of age or older with underlying multi-system disease. The major indications included infiltrates and retained secretions from ineffective suctioning or mucous plugging. The sterile, double-sleeved catheter significantly aided in the diagnosis of pneumonia in these patients. Elderly patients tolerated reasonable doses of premedication for bronchoscopy without the need to adjust the dose of their chronic medications. Local anesthesia with xylocaine produced a sufficient pharmacologic effect.

Bleeding (>20 cc) is a potential complication of any biopsy procedure, and the decision to proceed to forceps biopsy should be dictated by the overall visualization of the endobronchial tree for the presence of increased mucosal friability. Fever may have been related to microatelectasis or retained secretions, but was self-limited. Although dysrhythmias were infrequent, continuous oxygen therapy and electrocardiographic monitoring in these patients during and up to two hours after bronchoscopy is recommended. Finally, given the safety of bronchoscopy in the elderly patients in this report, a prospective study should be performed to determine its safety in such patients in the outpatient setting, where most bronchoscopies occur.

Acknowledgments. Dr Donald Zavala reviewed the manuscript, and Mrs Eleanor Mangieri provided secretarial assistance.

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The influence of race and other factors on the outcome of intracranial surgery for cerebral artery aneurysms

DAVID M. KAUFMAN, MD, RUSSELL K. PORTENOY, MD, MARTIN L. LESSER, PhD,
KAMRAN TABADDOR, MD

ABSTRACT In a follow-up study of patients who underwent intracranial surgery for cerebral artery aneurysms, the rate of adverse events (combination of morbidity and mortality) was 28%—significantly lower than in our previously published study. In an analysis of the relative importance of prognostic factors, the occurrence of an adverse event was associated with a poor neurologic grade ($P < 0.08$), an age of 50 years or older ($P < 0.08$), and hypertension ($P < 0.04$). Allowing for other factors, race itself is not associated with an adverse event in intracranial surgery for cerebral aneurysms.

(NY State J Med 1984; 84:549–553)

INTRODUCTION

Previously, two of us (DMK and KT) reported the results of five years (January 1, 1971–January 1, 1976) of intracranial surgery for ruptured cerebral artery aneurysms at an urban medical center.[1] Differences between these results and those of other referral centers were attributed to the greater number of patients who were in poor neurologic condition prior to surgery, were 50 years of age or older, or underwent surgery within 14 days after a subarachnoid hemorrhage.

We have reviewed the results from the subsequent five and a half years (January 1, 1976–July 1, 1982). In particular, we have analyzed the factors that could influence outcome: the patient's sex, age, and race; the presence of hypertension; the interval between the subarachnoid hemorrhage and surgery; the location of the aneurysm; and the patient's condition before surgery.

The influence of race on the outcome was analyzed in detail. Its influence is considered alone and in combination with hypertension and each of the other variables.

PATIENTS AND METHODS

The records of all patients who underwent a craniotomy for a ruptured intracranial artery aneurysm between January 1, 1976 and July 1, 1982 have been reviewed. Cases of mycotic and traumatic aneurysms were excluded. The patients were cared for at the three major hospitals associated with the Albert Einstein College of Medicine: Bronx Municipal Hospital Center, Montefiore Medical Center, and the Hospital of the Albert Einstein College of Medicine. Surgery was performed almost entirely by three attending and chief residents in neurosurgery.

The demographic and other data were gathered from the patients' charts. The presence of hypertension was determined from the chart, although details of its chronicity or severity were usually not included. The preoperative conditions of the patients were reconstructed by a review of the record, and they were graded, similar to Botterell et al,[2] in the following manner: grade 1, alert without neurologic deficit; grade 1+, alert with central nervous system (CNS) deficit; grade 2, lethargic without CNS deficit; grade 3, lethargic with CNS deficit; grade 4, stuporous; grade 5, comatose. Grade 1+ was added to the basic classifications to accommodate patients in a "good" neurologic state.

The Hunt and Hess criteria[3] were not used because the Botterell system was employed in the initial review and because the Hunt and Hess criteria result in placement in a higher (worse) category if serious systemic disease—hypertension, for example—is present. This method would have obscured our data because the grading would have been influenced by the factors that were to be studied as independent variables.

An internal carotid or posterior communicating artery aneurysm was designated I; middle cerebral artery aneurysm, II; anterior cerebral or anterior communicating artery aneurysm, III. Patients with vertebrobasilar artery aneurysms were excluded.

A postoperative assessment was based on the patient's condition at the time of discharge, but if a patient was evaluated subsequently, results of the latter examination were used. Morbidity was judged to have occurred if motor or intellectual deficit appeared following surgery. Mortality was attributed to the surgery in all postoperative deaths. A category of "adverse outcome," developed for the purposes of this study, was used to designate the presence of either morbidity or mortality.

Each variable was cross-classified with the presence or absence of an adverse event as well as with the occurrence of morbidity or mortality. The data were analyzed in a univariate fashion, using either the chi-square or Fisher exact test. Multivariate analysis, using stepwise multiple logistic regression, was carried out to determine which factors, alone or in combination, could be used to predict an adverse event.[4]

Logistic regression—a statistical method by which the probability of an event (in this case, an adverse event) is modelled as a mathematical function of one or more variables[4]—was performed. The methodology allows one to assess the statistical significance of several factors, alone or in combination, in relation to the likelihood of an adverse event. Logistic regression can often be more valuable than many univariate analyses (in which each variable is studied by itself), since it can be used to evaluate the importance of a given factor after "accounting" for the influence of several other factors.

The result of a statistical analysis was reported and discussed in detail if $P < 0.10$. It was hoped that reporting results at the 10% level might aid in making comparisons to other investigations.

RESULTS

Characteristics of the sample. Tables I and II show the numbers and proportions of patients in various demographic and clinical categories. Salient findings were the following: black patients accounted for 43% of the sample; whites, 31%; and hispanics, 26%. Forty-four patients (37%) were men. Of the entire patient group, 79 (66%) were under 50 years of age.

Aneurysms of the internal carotid or posterior communicating artery (location 1) were the most frequent (58%). The majority of the patients were in good neurologic condition before surgery: 75 (63%) were classified as preoperative grade 1. The most frequent interval

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From the Departments of Neurology (Drs Kaufman and Portenoy), Biostatistics (Dr Lesser), and Neurologic Surgery (Dr Tabaddor), Montefiore Medical Center-Albert Einstein College of Medicine, Bronx, New York.

Address correspondence to Dr Kaufman, Associate Professor, Department of Neurology, Montefiore Medical Center-Albert Einstein College of Medicine, 111 East 210th St, Bronx, NY 10467.

TABLE I. Relationships of Demographic Factors to Post-Operative Outcome

	All Patients								Grade 1 Patients						
			Adverse Event*		Morbidity		Mortality			Adverse Event		Morbidity		Mortality	
Factor	No. of Patients	% of Sample	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	No. of Patients	%	No. of Patients	%	No. of Patients	%
Race															
white	37	31	10	27	5	14	5	14	23	4	17	2	9	2	9
black	51	43	15	29	12	24	3	6	32	8	25	7	22	1	3
hispanic	31	26	8	26	7	23	1	3	20	5	25	5	25	0	0
Sex															
male	44	37	13	30	11	25	2	5	24	4	17	4	17	0	0
female	75	63	20	27	13	17	7	9	51	13	25	10	20	3	6
Age[†] (yr)															
<50	79	66	18	23	11	14	7	9	48	7	15	6	13	1	2
50+	40	34	15	44	13	33	2	5	27	10	37	8	30	2	7

* An adverse event occurred if either morbidity or mortality occurred.

[†] $P < 0.09$ (All patients, adverse event); $P < 0.05$ (Grade 1 patients, adverse event).

of time between rupture and surgery was 8 to 14 days (45%), followed by 22 or more days (33%). Hypertension was reported in 43 (36%) of the patients.

The morbidity rate was 20%; mortality rate, 7%; and adverse event rate, 28%.

Relationships of factors to adverse events. Tables I and II show how the demographic and clinical factors related to the occurrence of an adverse event. Among all 119 patients and those in grade I, the incidence of an adverse event was significantly higher in patients 50 years of age and older ($P < 0.09$) and in patients with hypertension ($P < 0.04$). Although the trend was toward a higher likelihood of an adverse event with increasing grade, this result was not significant.

No other demographic or clinical factors were associated with the frequency of an adverse event.

Relationship of factors to race and hypertension. Several factors that were significantly associated with race are shown in Table III. White patients were older than their black or hispanic counterparts ($P < 0.03$). Black patients had a significantly higher incidence of aneurysms (69%) of the internal carotid or posterior communicating artery ($P < 0.03$).

More importantly, hypertension was observed significantly more often in black (57%) than white (22%) or hispanic (19%) patients ($P < 0.001$). Hypertension, however, was not associated with age: 37% of 79 patients with hypertension were less than 50 years of age, while 35% of 40 patients 50 years of age or older had hypertension (Table IV).

Using logistic regression, three variables were significantly associated with the occurrence of an adverse event, where b is the regression coefficient; SE, standard error; and P, probability: pre-operative grade (b = 0.60, SE = 0.35, $P < 0.08$), age (b = 0.83, SE = 0.44, $P < 0.08$), and hypertension (b = 0.95, SE = 0.43, $P < 0.04$). While race and hypertension were associated with each other, only hypertension

TABLE II. Relationships of Clinical Factors to Postoperative Outcome

	All Patients								Grade 1 Patients						
			Adverse Event*		Morbidity		Mortality			Adverse Event		Morbidity		Mortality	
Factor	No. of Patients	% of Sample	No. of Patients	%	No. of Patients	%	No. of Patients	%	No.	No. of Patients	%	No. of Patients	%	No. of Patients	%
Location of aneurysm															
I	69	58	19	28	14	20	5	7	45	11	24	9	20	2	4
II	18	15	6	33	5	28	1	6	11	3	27	3	27	0	0
III	32	27	8	25	5	16	3	9	19	3	16	2	11	1	5
Interval between rupture and surgery, days															
1-7	9	8	3	33	1	11	2	22	5	1	20	1	20	0	0
8-14	54	45	15	28	13	24	2	4	41	9	22	8	20	1	2
15-21	17	14	5	29	5	29	0	0	11	3	27	3	27	0	0
22+	39	33	10	26	5	13	5	13	18	4	22	2	11	2	11
History of hypertension[†]															
No	76	64	16	21	12	16	4	5	49	8	16	7	14	1	2
Yes	43	36	17	40	12	28	5	12	26	9	34	7	27	2	8
Grade															
1	75	63	17	23	14	19	3	4	Not applicable						
1+	37	31	13	35	8	22	5	14							
2, 3	7	6	3	43	2	29	1	14							

* An adverse event occurred if either morbidity or mortality occurred.

[†] $P < 0.04$ (All patients, adverse event); $P < 0.09$ (Grade 1 patients, adverse event).

TABLE III. Relationship of Race to Clinical and Demographic Factors

	White Patients		Black Patients		Hispanic Patients	
	No.	%	No.	%	No.	%
Total	37	100	51	100	31	100
Factor						
Location*						
I	18	49	35	69	16	52
II	4	11	5	10	9	29
III	15	40	11	21	6	19
Grade						
1	23	62	32	63	20	65
1+	12	32	15	29	10	32
2, 3	2	6	4	8	1	3
Interval,† days						
1–7	2	5	3	6	4	13
8–14	12	32	24	47	18	58
15–21	5	14	7	14	5	16
22+	18	49	17	33	4	13
History of hypertension‡						
No	29	78	22	43	25	81
Yes	8	22	29	57	6	19
Age†						
<50	18	49	38	75	23	74
50+	19	51	13	25	8	26
Sex						
Male	18	49	17	33	9	29
Female	19	51	34	67	22	71
Adverse event	10	27	15	29	8	26

* $P < 0.03$.
† $P < 0.10$.
‡ $P < 0.001$.

was a significant predictor of an adverse event. In the univariate analysis in Table II, grade was not a significant factor; however, with logistic regression analysis, and a given hypertension status and age, increasing grade is associated with the occurrence of an adverse outcome.

Using the fitted logistic model, the estimated probability of experiencing an adverse event was 2.6 times greater for a patient with hypertension than for a patient with normal blood pressure, 2.3 times greater for patients 50 years of age or older, and 1.8 times greater as a patient's grade changed from 1 to 1+ or from 1+ to 2 or 3.

Interactions among factors were also tested, but were not statistically significant. In particular, the effect of preoperative grade was the same in patients with and without hypertension. Also, despite hypertension being more prevalent in black patients, the adverse event rate was still higher in older (46%) than younger (24%) black subjects.

Comparison with previous study. A comparison of the present study to the previous one[1] is outlined in Table V. Although any comparison is fraught with problems, several conclusions can be drawn. The adverse event rate is significantly lower ($P < 0.003$) in the present study (28%) compared to the previous study (46%). An adverse event was significantly less frequent ($P < 0.01$) in older patients in the present study (38%) than in the previous study (64%). Although the adverse event rate was lower for surgery performed in the first seven days in the present study (33%) compared to the previous study (63%), the number of patients was not large enough to be statistically significant. The improvement in outcome when surgery was performed in the second week (28% versus 44%) was, however, significant ($P < 0.10$).

DISCUSSION

The results show an improvement in the outcome of intracranial surgery for cerebral artery aneurysms in this study compared to our initial study.[1] Given the advances in medical care, such a beneficial trend is expected, but it is rarely documented.[5,6]

Several authors have attributed improvements to various technical innovations:[6–8] (1) improved lighting, instrumentation, and surgical magnification; (2) use of newer anesthetic agents and techniques that provide controlled hypotension and maintain optimal cerebral perfusion and oxygenation; (3) management of postoperative cerebral vasospasm with fluids and medications; (4) surgical intervention within 48 or 72 hours of aneurysm rupture in patients who are in good neurologic condition.

Improved results were obtained because of these innovations as well as a tendency to operate only on patients in good neurologic and medical condition. In particular, in the initial study only 51% of the patients were in good neurologic condition (grade 1), but in the present study 63% of patients were in comparably good condition. There may also have been fewer patients with hypertension in the latter study.

Another reason for the improved results may be that since the conclusion of the first study, only three neurosurgeons have been doing virtually all of the surgery, whereas previously the patients were distributed among at least six attending neurosurgeons and 10 senior house officers. Others have also noted that surgical results are probably better if cases of ruptured aneurysms are cared for in referral centers by specialized teams,[9] although excellent results have been reported by surgeons who perform aneurysm surgery on an infrequent basis.[10]

In the present study, by employing the terms "adverse event" to denote the presence of postoperative morbidity or mortality, and using sophisticated statistical procedures, we have determined the effect of three factors: age, hypertension, and race. In our previous study, we demonstrated that the mortality rate of patients who were 50 years or older was double that of younger patients. Likewise, in the Cooperative Study,[11] patients in good preoperative condition (grades 1 or 2) who were aged 50 years or above had a mortality rate of 44%, but those younger had a mortality rate of 25.5%. Sengupta et al,[12] found that three quarters of the patients aged 60 to 65 years can have surgery without risk of major neurologic deficits, and Ohmoto et al[13] found that morbidity and mortality rates were similar in aged patients who were in good neurologic condition. The present study demonstrated that the increased incidence of adverse outcome remains significantly higher ($P < 0.01$) among the older age group even if other variables are excluded from the analysis.

The adverse influence of hypertension on outcome is found in most studies, although not in one by Samson et al.[14] While a group at the Mayo Clinic[9,15] found little relation-

TABLE IV. Relationship of Hypertension to Age

	<50 years of age	≥50 years of age	Total
Number of patients	79	40	119
Number (%) with hypertension	29 (37)	14 (35)	43 (36)

TABLE V. Comparison of Postoperative Outcomes: Present Series versus Previous Series*

	Present Series							Previous Series						
		Adverse Event		Morbidity		Mortality			Adverse Event		Morbidity		Mortality	
	No. of Patients	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	No. of Patients	%	No. of Patients	%	No. of Patients	%
Group														
All patients[1]	119	33	28	24	20	8	7	123	57	46	34	28	23	19
Grades[2] 1, 1+	112	30	27	22	20	8	7	63	29	46	21	33	8	13
Age 50+[3]	40	15	38	13	33	2	5	44	28	64	16	36	12	27
Interval from rupture to surgery, days														
1–7	9	3	33	1	11	2	22	24	15	63	6	25	9	38
8–14[4]	54	15	28	13	24	2	4	43	19	44	11	26	8	19
15–21	17	5	29	5	29	0	0	32	15	47	12	38	3	9
22+	39	10	26	5	13	5	13	19	5	26	3	16	2	11

* Comparison of adverse event rates, present versus previous series: [1] $P < 0.003$; [2] $P < 0.01$; [3] $P < 0.02$; [4] $P < 0.10$.

ship between hypertension and onset of a subarachnoid hemorrhage, they did find that hypertension could be used to predict the outcome once an aneurysm ruptured. Ljunggren et al,[16] suggesting that patients with hypertension are more vulnerable to arterial spasm, found that these patients had a 50% mortality rate compared to a 6% mortality rate for patients who do not have hypertension. In the Cooperative Study,[17] with patients in good neurologic and good general medical condition, 55.5% of those with hypertension died compared to 25% of the same group without hypertension.

Overall, patients with hypertension were significantly more likely ($P < 0.04$) to contribute to the morbidity or mortality statistics. The rate of an adverse event was 2.6 times greater than in patients without hypertension. More importantly, the effect of hypertension was more significant than either the neurologic grade or patient age. The effect of hypertension, noted in 36% of patients, is dramatic when seen in combination with the effects of age and grade (Fig 1). Hypertension was not related to age per se (Table IV).

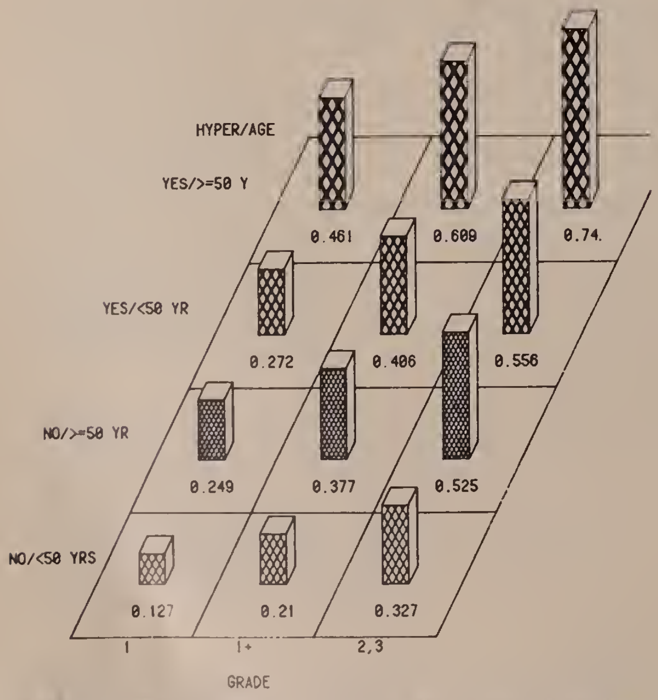

FIGURE 1. Surgical treatment of cerebral aneurysm: estimated probability of adverse event based on logistic regression model.

Black patients comprised 43% of the sample, white patients 31% and, hispanic patients 26%. The rate of adverse outcome was not statistically different among these groups. There were several differences in demographic or clinical variables, but these did not significantly alter outcome. Black patients, for example, had a greater incidence of internal carotid or posterior communicating artery aneurysms.

The most salient differences between the races were the incidences of hypertension and older age. Significantly ($P < .001$) more black patients had hypertension than white or hispanic patients. White subjects were more often older than 50 years than black or hispanic subjects ($P < 0.03$). Logistic regression analysis showed that hypertension and age were both predictors of adverse outcome. Though these variables were significantly associated with different races, no difference by race was found, perhaps due to a balancing of influences. In other words, the outcome of a black patient was burdened by hypertension, and that of the white patient by age. More importantly, when these other factors were statistically controlled, this lack of difference among races was confirmed.

Acknowledgments. Drs Robert Katzman, Hugh Wisoff, Seymour Solomon, and Herbert Schaumberg assisted in reviewing the manuscript prior to submission for publication.

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Clinical medicine will change for physicians everywhere in the United States, owing to advancing biomedical knowledge and to the development of newer diagnostic and therapeutic technologies and modalities. The structure of medical practice, as well, will change because of economic, social, and political forces and public policy decisions. But for physicians in places like New York City the structure of medical practice will also change in response to local social and economic trends. Changes of this kind and magnitude are always unsettling, but physicians now practicing in the city are already veterans of change; those of lesser heart fled to the supposed safety of the suburbs long ago.

Because the recent changes have been so heavily negative is no predictor that they will always be so. Although New York City continues to lose commerce and industry as well as its cultural assets, there is still no other place in the country with as much to offer. The well is far from running dry, and the exodus trend may not continue.

We can, I think, take some solace in the fact that changes and trends occur in cycles. Life, after all, did improve for man after the ice ages, but few who experienced those times would have hazarded such a prediction. Medicine and the practice of it face exciting frontiers and challenges in New York City. Those of us who choose to stay and face them are, according to the Chinese the recipients of the greatest blessing. We live in interesting times.

PASCAL JAMES IMPERATO, MD
(*NY State J Med* 1982; 82:945)

A review of The Administration of a Public Health Agency, *an incisive study of the New York City Department of Health, by Dr Imperato, Deputy Editor of the* Journal *is found on page 578.*
—Editor

Opposition to compressed tablets in 19th and early 20th century medicine

JOHN S. HALLER, JR

Over the centuries, physicians have employed various techniques to introduce medicines into the body—from anointing and inunction to injection with hypodermic syringes, inhalation, absorption of medicated substances into the tongue, and treatment by mouth, rectum, vagina, and other cavities. Each of these techniques has had its own rich history of development and usage. While some were borrowed from earlier cultures and peoples, others were indigenous to western medicine.

No innovation, with the possible exception of the syringe, was as revolutionary in its impact as the development of the compressed tablet. Like other forms of medication, its history is replete with both defenders and critics, and the issues surrounding its use resulted in a brief yet serious debate within medical circles that questioned some of the very premises of medical education and existing health care delivery systems.

FORMS OF MEDICATION

Prior to the introduction of the compressed tablet, physicians could use a number of medication techniques. One popular form, known as endermic medication, employed animal, vegetable, mineral, and mechanical vesicants—a mode that required removing the cuticle and applying the remedy to the denuded surface. This technique was popular from ancient times through the first half of the 19th century. Although seldom used since then, it was a popular method for treating intermittent diseases, common ague, fever, chronic neuralgias, and sciatica. Variations of the endermic method included inunction (applying an ointment), moxa (a technique of raising a blister with fire), cautery (applying heated metal irons), and boiling water.[1]

When the patient was unable to swallow due to strictures, ulcerations, cancer or tuberculosis involving the esophagus, pharynx, or larynx, physicians introduced medicines via the rectum. Body cavities such as the vagina, urethra, ear, and nose were used primarily for local rather than constitutional or systemic effects.

Inhalation was used to induce a local effect on the mucous membranes of the nasal fossae, pharynx, larynx, trachea, and bronchial tree. In cases of consumption and asthma, however, physicians preferred the constitutional effect of inhaling warm vapors charged with boric acid, or smoking stramonium leaves. In another variation of inhalation, that of insufflation, medicines were introduced in powder form instead of a smoke or spray—a technique that compared to the inhaling of snuff. Another type of insufflation consisted of blowing or dusting iodoform or similar medications on external surfaces and wounds. An example of this was the mercurial vapor bath which doctors employed for its constitutional effect, typically in cases of syphilis.[2]

The syringe, introduced in the second half of the 19th century, enabled drugs to be administered and to take effect more promptly. Despite the smaller amount of medicine injected, the syringe ensured quick response, particularly in cases where timing was important. The disadvantages to the hypodermic method included the need for a physician to administer each dose. Moreover, infection, overdosage, irritating local effects, and abscesses were common in the early days of its use, especially in the years prior to asepsis and germ theory. Examples of erysipelas, septicemia, injections directly into a vein, clotting, and the complications of embolism were frequent occurrences in the early years.[3-6]

The most popular mode of administering medication was by mouth, a method used by patients and attendants alike, and which allowed for measured doses in quantities appropriate to individual need. There was, however, a tendency among physicians to prescribe anything that could be chewed, drunk or swallowed whole. As a result, nauseous and incompatible boluses, infusions, decoctions, tinctures, extracts, powders, salts, and oils were prescribed with a feverish intensity that knew few bounds. The harshness of many of these drugs no doubt drove some patients to alternative treatments by faradic, static, and galvanic electricity, massage, or the phantom promises of homeopathy, hydropathy, Christian Science, and other sectarian practices.

THE COMPRESSED TABLET

During the second half of the 19th century, physicians

Address correspondence to Mr Haller, Department of History, California State University at Long Beach, 1250 Bellflower Blvd, Long Beach, CA 90840.

turned increasingly to compressed and molded tablets as a medium that avoided spillage, encouraged more exact dosage, ensured uniformity in weight and appearance, and proved more portable. Although introduced as early as 1843 by William Brockeden of England who patented a machine (English patent no. 9977) designed for compressing tablets, lozenges, and black lead for pencils, use of compressed tablets did not become widespread until the late 1870s and early 1880s. One might assume that their introduction came with the full blessing of physicians, and that they were spread evenly across the medical landscape, but the reality was quite different. As with any labor-saving innovation, the compressed tablet was perceived as both friend and foe. The resulting dialogue did little to diminish the trend toward the manufacture and dispensing of tablets; however, it did serve for a time to provide a platform for critics, allowing them to question the preparation of compressed tablets within the context of medical education and the direction of health care delivery systems.[7–9] (Figs 1, 2)

Given the various forms available for administering oral medicines, critics were not at all convinced that tablets offered an improvement in effectual delivery. Representative of this attitude was Otto Wall, MD, who, writing in 1882, argued that tablets offered too small a surface for the stomach to act upon and, even if dissolved, delayed effective action. Moreover, the concentrated form of medicine often irritated the mucous membranes, producing unexpected and sometimes detrimental side-effects. The class of preparations which Wall, a professor at the St Louis College of Pharmacy, preferred above all others, was the fluid extracts. According to Wall, these combined all the advantages and few of the disadvantages of oral medications. They were readily absorbed and reasonably compact, yet they provided a maximum surface for action in the stomach and intestines.[1]

Even physicians who were supportive of the tablet warned against its use in illnesses requiring immediate relief, where irritation of the stomach and bowels might result, or where the intestinal juices might not produce the desired effect. One physician reported a case in 1882 of a patient suffering from congestive chills for whom the administration of medicines in tablet form represented "criminal malpractice." The patient, he claimed, had been too weak to digest the tablets, which therefore proved ineffective in meeting the crisis.[10]

The portability and convenience of the compressed tablet did not go unnoticed by the American military. In 1891, both the Army and the Navy awarded a contract for developing a new system of carrying medical and surgical supplies. The impetus for a new system had grown out of the last Sioux campaign, with the subsequent need for medical supplies in a more compact and portable form, with greater security and economy. The contract resulted in the development of a wooden chest that weighed 85 pounds and contained 60 bottles of compressed tablets. If the contents of the chest had been in liquid form, remarked J. C. Merrill, MD, of the Surgeon-General's Office, "their customary jars and bottles . . . would occupy nearly one half of the space of a regular freight car." Each battalion of 200 men was sent two such chests to be placed under the driver's seat of an ambulance or suspended on each side of a pack mule. Merrill supervised the experiment with the chests, and claimed that the new system revolutionized the mode of supplying the armed services. Only whiskey, brandy, alcohol, and castor oil remained to be carried in liquid form.[11]

FIGURE 1. Hand punch and die for compressing pills.

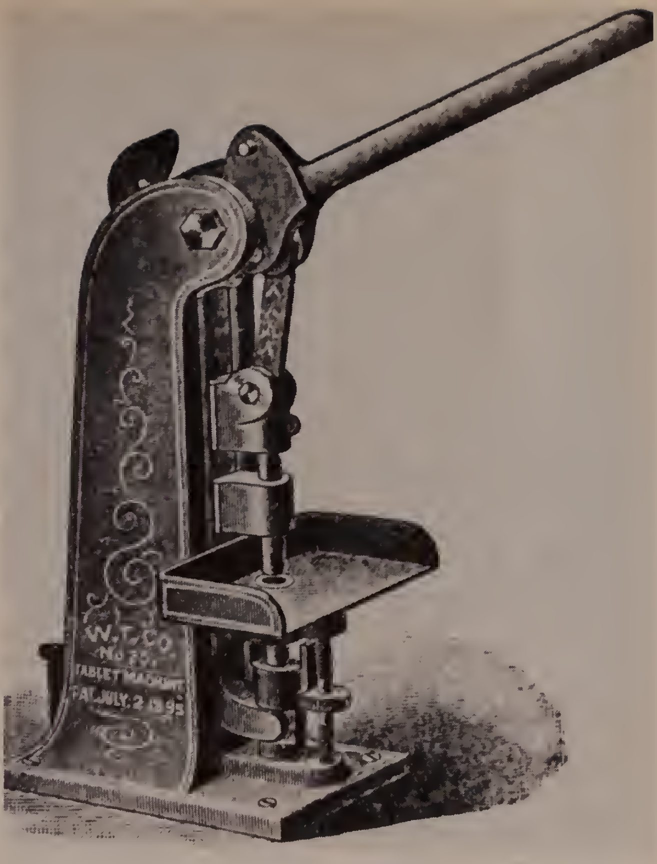
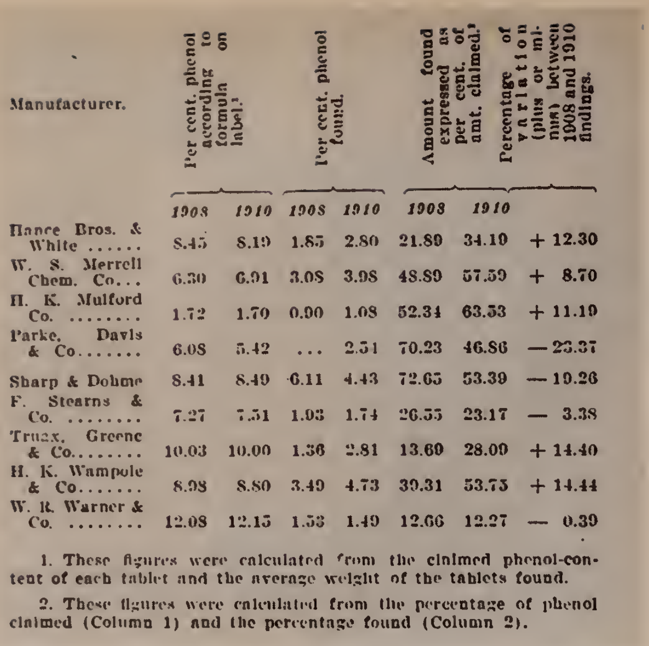


FIGURE 2. Whitall, Tatum Co's pill compressing machine.

Studies undertaken in 1908 on the reliability of tablet content indicated that compressed tablets sold by different pharmaceutical firms contained amounts of drug ranging from 12.66% to 72.65% of the amount stated in the formula. A later study in 1910 showed that while the products of some firms had improved in the two-year period, others were worse than before[12] (Fig 3).

According to E. B. Patterson, the results of the 1910 study caused him to be "called on the carpet" by Parke, Davis and Co, since he was foreman of the company's tablet manufacturing department. He was instructed "to spare no expense nor trouble to make each preparation . . . the best of its kind, both in the exactness of its compounding and



Manufacturer.	Per cent. phenol according to formula on label.[1]		Per cent. phenol found.		Amount found expressed as per cent. of amt. claimed.[2]		Percentage of variation (plus or minus) between 1908 and 1910 findings.
	1908	1910	1908	1910	1908	1910	
Hance Bros. & White	8.45	8.19	1.85	2.80	21.89	34.19	+ 12.30
W. S. Merrell Chem. Co...	6.30	6.91	3.08	3.98	48.89	57.59	+ 8.70
H. K. Mulford Co.	1.72	1.70	0.90	1.08	52.34	63.53	+ 11.19
Parke, Davis & Co.......	6.08	5.42	...	2.51	70.23	46.86	— 23.37
Sharp & Dohme	8.41	8.49	6.11	4.43	72.65	53.39	— 19.26
F. Stearns & Co.	7.27	7.51	1.93	1.74	26.55	23.17	— 3.38
Truax, Greene & Co........	10.03	10.00	1.36	2.81	13.60	28.00	+ 14.40
H. K. Wampole & Co.......	8.98	8.80	3.49	4.73	39.31	53.75	+ 14.44
W. R. Warner & Co.	12.08	12.15	1.53	1.49	12.66	12.27	— 0.39

1. These figures were calculated from the claimed phenol-content of each tablet and the average weight of the tablets found.

2. These figures were calculated from the percentage of phenol claimed (Column 1) and the percentage found (Column 2).

FIGURE 3. Comparison of drug amounts stated in formulas and amounts found in tablets (*JAMA* 1910; 55:2169).

in pharmaceutical elegance."[13] In his subsequent investigation, he found large discrepancies in the quantity of ingredients stated on the label and that contained in the tablets, the greatest variation being among the smaller tablets. "Analysis of goods on hand," he noted, "showed them all deficient and, worst of all, no one could even suggest an explanation." He discovered that no matter how carefully the ingredients were weighed, a production cycle that was designed to produce 28,000 1/4-gram tablets inevitably resulted in 34,000.

> This thing went on day after day until the entire department was upset; finally, after studying this matter for days, I was sitting by one of the tables watching the girl work and I noticed that from time to time she would pick up a small camel's hair brush and dipping it in a pile of terra alba [dusting powder] on her table would, very lightly, brush over the strips and partly cut pills . . . By weighing the supply before using and again after a pound had been cut, it was found that ½ ounce of this powder was consumed in cutting 1 pound of mass into ¼ gr. pills. This meant 218 grains, which divided into ¼ gr. pills, made an addition to the written formula of 872 pills and we had found the leak which had been going on for years.[13]

In addition to problems of quality control in the manufacturing process, there remained the issue regarding the relative rate of disintegration, which seemed not to have concerned the early makers of tablets. One physician remarked in 1877 that his favorite tonic and bloodmaking tablet, which was composed of quinia, iron of hydrogen, arsenious acid, and strychnia, refused to dissolve in patients' stomachs. Instead, he found in their evacuations "spherical bodies resembling bullets."[14] As late as 1917, William Maske reported that tablets used in his experiments had taken from four minutes to eight hours to disintegrate.[15]

In those instances where physicians desired to have a medicine pass through the stomach and dissolve in the intestines, tablets with sugar or gelatine coating, or konseals, were of little value. Keratin, a chitinous substance derived from feathers, provided an appropriate covering for the salts of mercury, gold, iron, arsenic, creosote, salicylic acid, tannin, and alum. Some physicians preferred a mixture of shellac and salol dissolved in alcohol, which was then spread in a thin layer over the tablet. Tests with methylene blue showed that the covering remained undisturbed in the stomach and only dissolved in the small intestine where it served as an internal antiseptic. Gluten was another substitute, although thought by some to be ineffective since it tended to swell when in the stomach for any extended period of time. Tablets coated first with wax and then with gluten were considered preferable to keratin or gluten coating.[16-17]

As life insurance companies could attest, not all tablets were designed for consumption. Manufacturers also provided germicidal tablets made of bichloride of mercury for domestic and industrial use. According to the Metropolitan Life Insurance Company, the number of deaths from either accident or suicide using bichloride of mercury tablets amounted to 14.4% of the solid and liquid poisonings in 1917. Gray Phillips, MD, was sufficiently concerned with preventing accidental deaths that he developed a coating of wax that had a high melting point and was insoluble in water or digestive juices.[18] Tablets coated in such a manner passed through the alimentary tract unchanged, preventing any absorption of the tablet substance into the body. Only by breaking the tablet was it possible to prepare the germicidal solution. As an additional safeguard, he recommended giving the wax coating a distinctive color, or a bitter taste, which would serve as a warning to the person who accidentally attempted to chew the tablet.[18]

DECLINE IN THE ART OF WRITING PRESCRIPTIONS

By the turn of the century, concerned physicians on both sides of the Atlantic had taken note of the popularity among their colleagues of prescribing compressed tablets, and saw in their use a "slovenly and enervating habit of writing an order . . . and then identifying such an order with the title of a prescription." Critic Arthur P. Luff, MD, a physician at St. Mary's Hospital and lecturer on hygiene and forensic medicine in the medical school in London, was unable to dignify the practice of writing an order for a particular form of compressed drug with the term "writing a prescription."[19] Not only did he object to the assumption that what was good for one patient was also good for every other patient, he also warned colleagues that they were "playing into the hands, and the pockets, of the manufacturers of those preparations."[19] Moreover, physicians who drifted into the practice of ordering manufactured tablets simply encouraged patients to attempt self-treatment using readily accessible compressed tablets. In allowing this to occur, physicians were displacing the true therapeutic art with a medical delivery system that was in the hands of purely commercial interests—industrial pharmacists—functioning with all the prerogatives of the medical profession.

Harry R. Purdy, MD, a New York physician, wrote that individuals who had outstanding reputations in their respective medical specialties had allowed themselves to fall into the trap of fitting the disease to the remedy, rather than the remedy to the disease.[20] Stocking their offices with ready-made tablets, they prescribed in seeming disregard to the idosyncratic nature of illnesses and of patients. For Purdy, this was "but a cheap and undignified way of practicing medicine."[20] One result, he warned, was that patients were disinclined to return to the physician merely to receive a new supply of tablets. Instead, patients tended to seek the name of the tablet and then request it directly from the retail druggist.[20]

Critics blamed part of the problem on the pressures that large numbers of patients caused for hospitals; this necessitated the ordering of ready-made tablets prepared according to established formulas in the hospital pharmacopoeia. Although ordering tablets by name was perhaps justifiable by hospital standards, "since the student can always refer to the [hospital] pharmacopoeia for . . . the composition and strength of the medicine ordered," the same was not true for the profession in general. "There is no better method of acquiring a knowledge of correct dosage," wrote Luff, "than by hearing the physician or surgeon dictate his prescription, comment on the dosage . . . and give his reasons for the employment of such ingredients."[19] Left to their own devices, medical students would choose not to look up the composition of each medicine; forgetting to do so or simply avoiding the work involved in this repetitive act, they neither acquired the knowledge nor retained the information.

According to E. H. Colbeck and Arnold Chaplin in *The Science and Art of Prescribing*,[21] medical education offered little opportunity for the student to cultivate the art of writing prescriptions. Mastery of this art, which at one time was an indispensable component of the accomplished physician, "has languished under the influence of the pernicious habit of using ready-made formulae, more particularly those dispensed in the compressed form of tablet, tabloid, and the like, with which the market has been flooded in recent years."[21] Despite the fact that the dispensing of tablets was a timesaver for physicians and surgeons, not to mention the pharmacist, the unanticipated outcome of the new custom was that students and young doctors carried habits acquired in the hospital into private practice. Having lost confidence in their own ability to write a useful preparation, they soon fell "prey to the temptations offered them by manufacturers to prescribe some ready-made proprietary medicine or some form of a compressed drug."[19]

There is considerable literature in late 19th and early 20th century medical and pharmaceutical journals regarding the relationship between physician and druggist, and the accusations hurled by each regarding their proprietary rights and obligations. Through much of the name-calling, the pharmacist appeared to receive the brunt of the assault, accused of stealing patients, counter-prescribing, instigating opium and alcohol abuse, supporting the patent and proprietary medicine industry, advocating polypharmacy, and substituting drugs in prescriptions. Although there were two sides to each of these issues, with the physician conspicuously involved in each, the retail druggist faced the weightier burden of proof. Ironically, this seemingly one-sided onslaught tended to obscure the rise of industrial pharmacy and the vulnerability of the retail druggist.[22]

Few physicians were willing to point the accusing finger at themselves; nevertheless, exceptions did exist. In reviewing the many problems that plagued the medical profession, James Burnet, MD, a lecturer on practical materia medica and pharmacy, and registrar at the Royal Hospital for Sick Children in Edinburgh, concluded that the more he looked into the issues, the more he discovered "that the fault largely lies at our door."[23]

A particular area of culpability concerned the complaint that physician incomes were being reduced because druggists had chosen to prescribe over-the-counter. Burnet took particular exception to this claim, since, in his opinion, the root of the decline in physician income had been the decision by the physician to order ready-made medicines. Like Luff, he interpreted the term "prescription" to imply more than a simple order to the pharmacist to supply a given drug. A prescription consisted of four parts: the superscription—the letter Rx; the names of the substances to be administered, with their amounts; the directions for the dispenser; and the directions for the patient.[23]

Although Burnet chose not to deprecate the newer modes of treatment and of diagnosis, he nevertheless believed that the tendency among younger physicians to rely on serums and vaccines, blood counts, and instrumentation had occurred at the expense of the art of writing prescriptions. One telltale sign of this was the decline in the use of Latin by physicians in their directions to the druggist.

To make matters worse, the industrial pharmacist had begun publishing pamphlets that described various diseases, their symptoms, diagnosis, and treatment—in each case indicating the use of a certain compressed tablet. "For my part," commented Burnet, "I deem it to be a gross insult to the profession to which I have the honour to belong, and I shall continue to trample underfoot all such attempts at the instructing of medical men by laymen. The medical man rightly holds a place far above that of the manufacturing chemist, and the latter ought to be made to feel that in sending out such literature, better, perhaps, called waste paper, he is insulting the honourable recipient."[23]

THE AGE OF THE TABLET

Despite the opposition voiced from elements in the medical profession, by 1914, one fourth to one third of all medicines in the United States were administered in the form of tablets. The early years of the 20th century marked the beginnings of the age of tablet medication. So complete had been the assumption of tablet manufacture by the industrial pharmacist, that extemporaneous preparation of tablets by the retail druggist never amounted to much. The economy of scale that came with the cost of tablet manufacture eventually ruled out the making of prescription quantities by the local pharmacist.[24,25]

Additional factors that mitigated against the retail pharmacist making extemporaneous tablets concerned the equipment required for triturating, mixing, granulating, drying, lubricating, and compressing tablets; the need to break down crystals to form granules ready for compression; the appropriate use of starch or dextrin; the mixing of cacao butter shavings with the fine powders to make tablets of such substances as bismuth subnitrate, sulphur, calomel and charcoal; and the use of starch and Theobroma or liquid petrolatum in the making of sodium bicarbonate, sodium salicylate, and aspirin.[24,26,27]

In choosing to take refuge in ready-made tablets, physicians made a far-reaching advance from which few were willing to retreat. For the few vocal critics, this decisive step was the reason why doctors were growing poorer at the expense of the industrial pharmacist. For most physicians, however, the decision had permitted them to serve a broader clientele than ever before. Indeed, the health care delivery system had expanded by an almost geometric progression with this more simplified form of medication. The age of the tablet had arrived and, with it, medicine and pharmacy experienced dramatic changes.

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THE LIMITS OF A DRUGGISTS' RESPONSIBILITY

The following editorial appeared in the *New York Evening Sun*, July 16, 1906, and bears upon a question in which the medical profession, as the guardian of the health of the public, has a deep interest. It is to Dr. W. J. Cruikshank that both the profession and the public are under obligations for a persistent effort to secure for them a reasonable measure of justice in this case.

Apart from the immediate question of the injuries alleged by the plaintiff in the case of Laturen vs. the Bolton Drug Company, the application for permission to appeal made by Mr. James Taylor Lewis, counsel of the Medical Society of this State, is of extraordinary interest not only to the medical profession, but to the public generally, for it involves the large and important question of an apothecary's responsibility in filling a physician's prescription.

The prescription in this case called for *Elixir Pinus Comp. cum. Heroin* (*Merrell*). According to the testimony, the druggist, or his assistant, finding that he had none of this preparation, resolved, according to a not unknown tradition of retailers, to supply something "just as good." He had upon his shelves Merrill's Elixir Pinus Compositus, and seems to have argued plausibly to himself that the addition of heroin in the proper proportion was all that was necessary to effect a perfect fulfilment of the doctor's and patient's requirements. He therefore proceeded very conscientiously to find out exactly how much heroin was contained in each dose of the preparation prescribed, and having satisfied himself on this head added the requisite quantity. According to the doctor's testimony, the patient shortly after taking the medicine began to show marked symptoms of opium poisoning. Upon communicating with the druggist he learned what had happened, and to his mind the mystery of his patient's condition was satisfactorily accounted for. For, in the unqualified Elix. Pinus Comp. a certain quantity of the acetate of morphia is contained in each dose, whereas in the preparation prescribed by him, heroin is substituted in place of the morphia.

Now, the question whether the plaintiff in this case suffered as a consequence of the obvious error of the compounder or from some other cause is a matter of minor importance. What concerns the public is the right of a druggist to ignore a physician's orders and offer a substitute for a preparation which he does not happen to have. Moreover, the learned arguments of Judge Gaynor, who dismissed the complaint, have but a curious interest in consideration of the main issue. From a legal point of view, for instance, it may be very important that the doctor wrote "with" for *cum*, or *vice versa*, but this we beg leave to call a cavil. It is perfectly clear that his prescription called for a certain known preparation containing no morphine; it is perfectly clear that the druggist supplied a preparation that did contain morphine; it is perfectly clear that, according to Judge Gaynor's decision, the druggist was justified in doing so, that in effect he was justified in adding morphine to a prescription which did not provide for any. Here is the whole matter in a nutshell, and considering the effects that might follow substitution of this kind where morphine and other drugs are concerned, we say that apart from the consequences in this particular case the application for appeal is of singular interest to the public.

(*NY State J Med* 1906; 6:333)

A 32-year-old woman with a history of aortic aneurysm

CASE PRESENTATION

Richard Fuchs, MD (Assistant Attending Physician): A 32-year-old woman was brought to the emergency department of the New York Hospital in shock, and with severe pain in the left flank and left inguinal region.

At the age of 16 she was found at another hospital to have hypertension, with decreased blood pressure in the left leg; a renal angiogram suggested fibromuscular hyperplasia of both renal arteries. At that time an intravenous pyelogram was unremarkable, and screening tests for pheochromocytoma were negative. She was treated with diuretic therapy for the hypertension.

Sixteen months later, she delivered a stillborn, 16-week-old fetus. On physical examination, her blood pressure was 220/140 mm Hg, and an abdominal aortic aneurysm was noted. Angiography confirmed the presence of the aneurysm, as well as severe atherosclerosis of the distal aorta and iliac arteries. At laparotomy, an 8-cm abdominal aortic aneurysm was bypassed by a Dacron graft from the aorta to the left external iliac and the right common iliac arteries. A pathologic study indicated that the aortic tissue contained areas of fibrosis, chronic inflammation, and vasculitis; sections of a renal biopsy were unremarkable.

At age 24, aortography revealed increased and now marked dilation of the descending aorta above the graft. Over the next several years she was admitted repeatedly to another hospital because of uncontrolled hypertension, possibly related to poor compliance with recommended antihypertensive medications.

On her first admission to the New York Hospital at age 31, she had had prolonged fever, weight loss, and diffuse arthralgias. Blood, urine, stool, and sputum cultures were unremarkable; a chest roentgenogram, bone marrow studies, bone scans, liver and spleen scans, and serum levels of febrile agglutinins and anti-nuclear antibodies were all within normal limits. Serum transaminase levels were moderately elevated, and a liver biopsy showed nonspecific reactive hepatitis with poorly formed granulomas. The intermediate-strength purified protein derivative test for tuberculosis was positive, and a three-month course of isoniazid and ethambutol was continued until cultures of sputum and hepatic tissue were negative for mycobacteria.

Ten months before her final admission, she was readmitted with recurrent fever and a pulmonary infiltrate in the lower lobe of the left lung. Cultures were again negative, and a lung biopsy showed necrotizing vasculitis and granulomas suggestive of Wegener's granulomatosis. A repeat angiogram showed mild dilation of the ascending and arch segments of the aorta. The patient was treated with corticosteroids in high dosage, which was gradually reduced.

Four months later she was readmitted with severe back pain, fever, and chills. Again all cultures were negative. An abdominal sonogram showed no change in the aorta. The symptoms subsided with an increase in steroid dosage.

Three months prior to the final admission, she was admitted for evaluation of uncontrollable hypertension. The renin level in the left renal vein was 3 times that of the right. The left kidney was observed by radiography to be small, 8 cm. Following a nephrectomy of the left kidney, her blood pressure remained under control for approximately two months.

At that time, however, she was readmitted with a complaint of severe, tearing pain in the middle of her back. Her blood pressure on admission was 180/120 mm Hg. The patient's general appearance suggested Cushing's syndrome secondary to steroid therapy. A maculopapular eruption was present over the back and chest. There was no palpable lymphadenopathy. The lungs were clear on examination; there was a grade II/VI systolic ejection murmur audible at the base. Her abdomen was not tender; the liver was palpable 3 cm below the right costal margin, and the spleen was palpable 1 cm below the left costal margin. A midline abdominal mass was palpable and was thought to be an aortic aneurysm. There was no costovertebral angle tenderness; the peripheral arterial pulses were normal. No edema was present.

With high doses of propranolol and methyldopa her blood pressure decreased to 160/90 mm Hg. The abdominal sonogram was unchanged. The patient signed out of the hospital against medical advice, but continued on propranolol, methyldopa, and prednisone.

One month later, severe abdominal and back pain developed; when she was seen in the emergency department, she was in shock, with a palpable arterial blood pressure of 50 mm Hg, a tense abdomen with rebound tenderness, and a pulsatile abdominal mass. Emergency laparotomy was performed, but the patient's condition continued to deteriorate, and she died on the same day.

CLINICAL DISCUSSION

Stephen A. Paget, MD (Assistant Attending Physician):

Based on the clinicopathologic conference (CPC) held at New York Hospital-Cornell Medical Center, New York, NY, on October 4, 1983.

Clinical Discussion: Stephen A. Paget, MD, Assistant Attending Physician; *Radiology Presentation:* Elias Kazam, MD, Associate Professor, Department of Radiology; *Pathology Presentation:* Powers Peterson, MD, Assistant Attending Pathologist.

Editor: JOHN T. FLYNN, MD.

Address correspondence to Dr Flynn, Consulting Editor, *New York State Journal of Medicine*, PO Box 5404, 420 Lakeville Road, Lake Success, NY 11042.

In discussing this difficult diagnostic problem, we need to consider whether the patient had a single multisystem disease or more than one disease, in addition to considering the nature of the disease process or processes. This woman's illness spanned a period of 16 years, beginning at age 16; its catastrophic termination was related to the development of an abdominal mass, fever, shock, and severe pain radiating into the flank and groin. We must consider the possibility of a lesion in the genitourinary tract or other extraperitoneal organ system—perhaps a ruptured blood vessel or viscus, with bursting of the contents into the abdominal cavity or retroperitoneal space.

First, let us look back to the initial indications of serious illness at age 16, when cardiopulmonary abnormalities were detected: she had early onset of hypertension, atherosclerosis, and diminished pulsations and blood pressure in her left leg. These findings suggest diabetes and familial hypercholesterolemia—both with premature arteriosclerosis, or some type of congenital abnormality.

However, we are not informed as to the presence of hypercholesterolemia or diabetes; a family history of early atherosclerosis with myocardial infarction is not mentioned. One of the many angiograms performed suggested the presence of bilateral fibromuscular hyperplasia; however, the disease process was not limited to the renal or carotid arteries as would be the case with fibromuscular hyperplasia. She suffered from a more widespread vasculopathy which involved even the aorta. Therefore, I question a diagnosis of fibromuscular hyperplasia.

A patient with early-onset hypertension requires a clinical evaluation to rule out the secondary causes. In this case, Cushing's syndrome and pheochromocytoma were considered and appropriately ruled out. An intravenous pyelogram was done to see if renal artery stenosis might have reduced the circulation to one or both kidneys. Although the findings of this study were within normal limits, it is probable that some degree of stenosis had resulted in increased renin, angiotensin, and aldosterone levels, resulting in severe hypertension.

In many ethnic groups, especially in the Orient, early-onset hypertension may signal the onset of a systemic vascular disease, such as Takayasu's arteritis.[1,2] This unusual condition is an inflammatory disease of the aorta, especially of the aortic arch and its major branches. The pathologic lesions include inflammation and sometimes granuloma formation, leading either to stenosis or dilation of the vessels, or both. The symptoms will depend upon which organs suffer reduction of perfusion due to stenotic vessels.

During the period of the aborted gestation she was quite hypertensive, so the possibility of preeclampsia or eclampsia should be considered. In addition, it is possible that the vasculopathy that had reduced the circulation to the left leg and to the kidneys had also compromised the circulation to the reproductive organs, resulting in inadequate blood supply to the placenta and the early death of the fetus in utero. Such a situation is possible with congenital vascular disorders, severe atherosclerosis, or Takayasu's arteritis.

On physical examinaton and aortography a large abdominal aneurysm was found, which was treated surgically with bypass grafting. At that time, the angiogram was consistent with severe atherosclerosis of the distal aorta and of the iliac arteries. The question remained as to what type of initial pathologic insult had been sustained by the vascular intima which led to severe atherosclerosis. Was it a genetic or familial predisposition to atherosclerosis? Or was the initial intimal lesion only one aspect of a widespread process involving the entire thickness of the blood vessel wall? Certain disorders such as lupus erythematosus, pulmonary hypertension secondary to congenital heart disease, and Takayasu's arteritis can involve a combination of hypertension and vascular insult, which in turn predisposes the patient to the development of premature atherogenesis. I believe that some such process was at work here.

It is important to keep in mind that the renal biopsy was normal; this is particularly important when considering the diagnosis of Wegener's granulomatosis in the lung. It is possible to have a limited form of Wegener's granulomatous angiitis, but at the time of the renal biopsy there was no indication of glomerulonephritis, focal or proliferative, that would support the diagnosis of Wegener's granulomatosis. The pathologic study of the aortic tissue revealed chronic inflammation, fibrosis, and vasculitis, indicating the presence of an arteritis which could lead to stenoses, aneurysm formation, hypertension, and an interrupted pregnancy. These consequences further support the possibility of Takayasu's arteritis in this patient, in preference to another vasculopathy such as Wegener's granulomatosis, lymphomatoid granulomatosis, polyarteritis nodosa, and Churg-Strauss angiitis, all of which tend to affect the small or medium-sized blood vessels, and less so the aorta and its major branches. Other collagen vascular diseases can result in inflammation of blood vessels, but these disorders usually spare the very large vessels. Infectious diseases, including syphilis, can produce aortitis; despite the fact that syphilis predominantly affects the ascending aorta, it can be difficult to differentiate syphilis from Takayasu's arteritis based on gross examination and pathologic studies. In this case, the result of a serologic test for syphilis is not mentioned. However, the early involvement of the abdominal aorta makes me think that syphilis was not the cause of the arteritis in this case.

At 24 years of age, the patient was observed to have dilation of the descending aorta above the graft site. In all likelihood, the aorta, with its medial layer already weakened by vasculitis, was susceptible to further dilation by the hypertensive intra-aortic pressure proximal to the graft. Eventually, this condition could terminate in aortic rupture and sudden death.

During her illness, control of the hypertension with medication varied in its effectiveness, perhaps due in part to her non-compliance with medication regimes. Then, some 15 years after the onset of an apparent vascular disorder, a systemic disorder developed, manifested not by vascular abnormalities or ischemia, but by constitutional symptoms: fever, chills, weight loss, and arthralgias. Initially this problem was approached, from a diagnostic point of view, as a so-called fever of unknown origin (FUO). FUO is commonly accepted to be a fever of 100.8° F or higher over at least a three-week period, during which the cause of the fever remains undetermined despite appropriate diagnostic study. The term would seem to apply to this patient, and the question remains as to whether this FUO was part of the disease that began at age 16, was another superimposed disease, or was a condition that developed after the initial process had subsided.

It is of interest that in the presence of an otherwise negative diagnostic study for the cause of FUO, liver function tests were abnormal—presumably the serum glutamic oxalic and pyruvic transaminase levels and the serum alkaline phophatase level. An increase in alkaline phosphatase would have special importance, since in hepatic involvement in neoplastic and other systemic diseases such as sarcoidosis or tuberculosis, the serum alkaline phosphatase level may be elevated well before other tests become abnormal. Appropriately, a liver biopsy was performed; the pathologic findings included nonspecific hepatitis and granuloma formation. The latter is a collection of giant cells and macrophages with or without central necrosis and caseation, and may be an indication of a systemic disorder such as tuberculous infection or sarcoidosis. Other systemic causes of FUO are infections such as bacterial endocarditis, viral hepatitis, or fungal disease. Second only to infections as a cause of FUO would be neoplasms, such as lymphoma and leukemia, especially in association with joint pain accompanying the fever. Solid tumors, such as hypernephroma, should also be considered. However, there was no evidence for the presence of any of these neoplastic processes.

The next category of causes of FUO would be connective tissue diseases. In this patient, lupus erythematosus would seem unlikely because of the negative anti-nuclear antibody test and the prolonged clinical course without arthritis, serositis, skin rash, renal disease, or any central nervous system involvement. In addition, lupus involvement of large vessels rather than of smaller ones would be unusual. Similarly, rheumatoid arthritis would seem unlikely in the absence of typical findings involving the joints. Nor was there clinical evidence suggestive of dermatomyositis or scleroderma. Polyarteritis nodosa is a systemic vascular disorder associated with fever, neuropathy, skin vasculitis, organ infarction, and renal disease; although this remains a possibility, polyarteritis usually involves the small and medium-sized vessels most prominently. Wegener's granulomatosis is a granulomatous necrotizing angiitis. Because it was suspected on at least one occasion, it should not be discarded as a possibility.

Sarcoidosis can be a cause of FUO, particularly in a young black woman with granulomas seen on liver biopsy. In the face of the patient's clinical course, however, sarcoidosis seems not to coincide with most of the clinical problems presented here.

I believe that the clinical features of the FUO in this patient were most likely due to an infection. I am referring to the association of Takayasu's arteritis with tuberculosis, which has been reported so often in the Asian literature. It is true that the rate of positive purified protein derivative tests is high in the Orient, and therefore a significant relationship to Takayasu's disease is more difficult to prove. Nevertheless, it is important to be aware of the possibility of tuberculosis in association with this form of arteritis, especially when the latter has been quiescent for 15 years, and the patient then develops a systemic febrile illness. With Takayasu's arteritis, fever due to that disease alone usually occurs at the beginning of the illness and not later on in its course.

The protocol does not indicate the presence of a productive cough; cultures of the sputum and liver biopsy were eventually reported as negative for *Mycobacterium tuberculosis.* Ethambutol was discontinued, and isoniazid therapy was continued. Two months thereafter the patient had fever and a chest film showed an infiltrate in the lower lobe of the left lung. The lung biopsy at this time revealed a necrotizing vasculitis and granulomata, suggestive of Wegener's granulomatosis. Again, however, I question that impression. While Takayasu's arteritis may coexist with other forms of connective tissue disease, it is not likely to become transformed into the appearance of Wegener's granulomatosis. The pathologist may have been seeing an area of tuberculosis or other local infection that involved the arteries. With negative cultures for tuberculosis, I am still in doubt as to what the final pathologic specimens will reveal. I must accept, however, the pathologist's report of the presence of an angiitis. Also, the angiographic studies in general indicated involvement of all layers of the aorta throughout its length, although the patient appears not to have developed aortic insufficiency.

Six months prior to the last admission, she complained of fever, chills, and severe back pain; diagnostic evaluation did not reveal a definite cause, and the sonogram showed no change in the abdominal aorta. Her symptoms appeared to respond to an increase in steroid dosage. Can the back pain be attributed to osteomyelitis of the vertebral column, or to infection in the retroperitoneal area, including portions of the aorta, the periaortic lymph nodes, and the kidneys? Could a lesion in any of these tissues have caused the fever and chills? Yet the sonogram suggests no change in the organs in that region.

Three months prior to the final admission she had severe hypertension, and clear evidence of stenosis of the left renal artery, with an abnormally high level of renin secretion from the left kidney. A left nephrectomy appeared to alleviate the problem of the severe hypertension, but we are not told the results of the pathologic study of the resected kidney. Even though there are rare instances of Wegener's granulomatosis limited to the lungs, pathologic study of the resected kidney would in all probability have revealed a focal necrotizing glomerulitis, if indeed Wegener's disease was responsible for the prolonged febrile illness. I have difficulty in believing that the clinicians accepted Wegener's granulomatosis as being responsible for the FUO, and at the same time treated the patient only with steroids, without additional appropriate chemotherapy such as cytoxan.

Two weeks prior to her death, the patient was admitted with a painful tearing sensation in the back, but a sonogram showed no change. Her hypertension was treated medically, and she signed out of the hospital against medical advice. A tearing pain across the back suggests damage to a blood vessel, possibly a dissecting aneurysm of the aorta, which is often associated with this type of a sensation in the chest radiating through to the back. Alternatively, a process of tearing can originate in the vicinity of a vessel or a viscus, and subsequently involve either type of organ. Local infection in the retroperitoneal area, the periaortic area, or even the vertebral column must be considered.

On her final admission, she complained of abdominal and back pain, and had a tense abdomen, rebound tenderness, and a pulsatile abdominal mass. Clearly, some catastrophic event had taken place, possibly the rupture of a viscus or an aneurysm.

In summary, I believe that this young woman had Takayasu's arteritis, with development of a diffusely dilated aorta, and an aortic aneurysm which ruptured, causing death. But did she have another systemic illness superimposed on this arteritis in its later stages? I do not believe that she had Wegener's granulomatosis, but rather that tuberculosis was the cause of the later febrile illness. Tuberculosis may have involved the paravertebral region and may have contributed to the erosion of the aorta.

RADIOLOGY PRESENTATION

Elias Kazam (Associate Attending Radiologist): I will limit my comments to selected films taken of the patient, since a full review would be extremely time consuming. On the abdominal film, the spleen appears enlarged, and the stomach is compressed between the spleen and another soft tissue density. The sonogram indicated marked dilation of the upper abdominal aorta and superior mesenteric artery. The aorta is narrower at and above the level of the diaphragm; nevertheless, the dilation involved the entire aorta. The lumen of the aorta contained mural thrombi, to an extent which we cannot determine accurately. The aortogram performed 10 months prior to her death confirmed the aortic and arterial dilation (Figs 1, 2), including the renal and common iliac arteries; the inferior vena cava is markedly compressed by the aorta. The graft involving the lower aorta is not clearly seen.

On the computerized tomographic (CT) scan, prior to the nephrectomy, the left kidney appears small, as compared to the right. The spleen is enlarged, and the large mass noted on the abdominal film corresponds to a dilated aorta. The superior mesenteric artery is also dilated. Although I saw several abdominal sonograms on this patient, I did not consider Takayasu's arteritis, because the most common finding on arteriograms in that condition is vascular narrowing, rather than dilation.

The arteriograms outlined the sinuses of Valsalva, the ascending aorta, and the aortic arch, which do not appear dilated, but are irregular in outline. There are areas of relative dilation and areas of relative narrowing with straight contours. The origin of the left subclavian artery from the arch is partially constricted. The abdominal portion of the aorta becomes very tortuous as it descends, again with areas of dilation and narrowing. Since only the lumen of the graft is opacified, the diameter of the aneurysm cannot be assessed on the aortogram but is visible on the sonogram. The lower iliac segments appear quite straight, as one would expect in the opacified regions of the iliac bypass grafts; even in these regions, however, the aneurysm could be present, as suggested by the sonogram but not demonstrated by the intravascular contrast study.

In summary, this patient had an irregularly outlined thoracic aorta and aortic arch with areas of narrowing and relative dilation, a feature that can be seen in Takayasu's arteritis; but the appearance of dilation of the abdominal

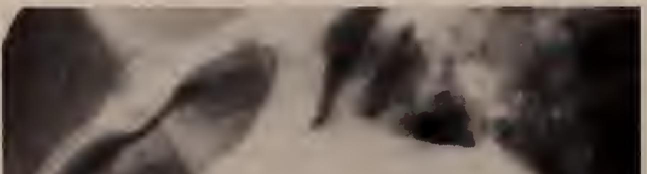

FIGURE 1. Aortogram showing irregular outline of aortic arch with areas of relative dilation and narrowing.

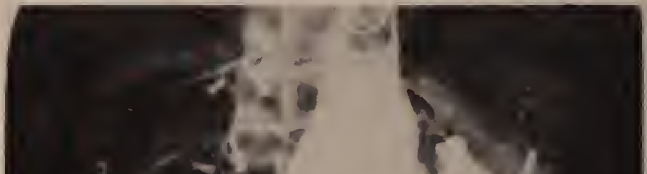

FIGURE 2. Tortuosity, dilation, and narrowing of abdominal aorta, with dilation of major aortic branches.

aorta would be unusual for that condition. All the major vessels arising from the aorta were dilated; the spleen and liver were enlarged; the left kidney was smaller than the right.

In her final admission, with the occurrence of tearing back pain, the sonogram showed no change; however, in the case of a suspected rupture of a retroperitoneal vessel, the definitive diagnostic study is not by means of a sonogram, but rather with the use of the CT scanner. With retroperitoneal bleeding there may be infiltration of the retroperitoneal fat, making sonographic evaluation difficult. In addition, the resulting adynamic ileus of the small bowel may further obscure the sonographic findings.

CLINICAL DIAGNOSES

Takayasu's arteritis.

Tuberculosis, probably miliary, involving many organs.

Possible erosion of retroperitoneal structures (viscera, blood vessels), secondary to Takayasu's arteritis or tuberculosis, with rupture and death.

PATHOLOGY PRESENTATION

Powers Peterson, MD (Assistant Attending Pathologist): I will review later, during my presentation of the autopsy findings, the results of the lung biopsy done at this hospital, on which the diagnosis of Wegener's granulomatosis was suggested. Before detailing the autopsy findings, I should mention that connective tissue stains of a medium-sized muscular branch of the aorta, obtained during the aortic bypass graft procedure, showed a striking proliferation of the vascular intima, with loose myxoid tissue. The media was markedly thickened and the adventitia, surprisingly by contrast, was very thin. An elastic stain of a second artery obtained during the same operation showed marked disruption and fragmentation of the elastic media, again with marked intimal proliferation. These changes are consistent with a healed arteritis, but they do not reveal the underlying cause. This intimal proliferation can be seen in almost any healed arteritis and is a secondary process, except in rheumatoid arteritis, which is the only true panarteritis. In this case, the healed vasculitis suggests a different condition; there is involvement of the aorta and the medium-sized arteries by a pathologic process that Dr Paget correctly indicated as Takayasu's arteritis.

Takayasu's arteritis is a condition that involves both inflammatory and reparative processes. The etiology of the condition is unknown, but is thought to have an autoimmune basis. It can affect the entire aorta from the sinuses of Valsalva to the femoral arteries, as well as the proximal portions of the major aortic branches and the pulmonary arteries. As with other suspected autoimmune processes, it is more common in young females. It exhibits a ratio of 10 female patients to one male patient, which is the opposite of the ratio of 10 male patients to one female patient characteristic of polyarteritis nodosa.

The initial clinical features of the condition usually include fever, malaise, and arthralgias. In the chronic or occlusive stage of the condition, which is also known as occlusive thromboaortopathy, the patient may experience vertigo, headache, and visual disturbances related to retinal artery involvement.[3] In 1908, a Japanese ophthalmologist, Takayasu, first described retinal arterial changes in a young woman[4]; and, for many years, it was thought that this disease was confined to the aortic arch. Loss of peripheral arterial pulses, however, can occur as the disease progresses; this is especially true for the radial pulses, due to involvement of the brachiocephalic arteries. Consequently, the condition has been identified by the name of "pulseless disease." Patients can develop hypertension, since the renal arteries are often severely affected. They may also experience intermittent claudication of the lower extremities, again due to vessel occlusion.

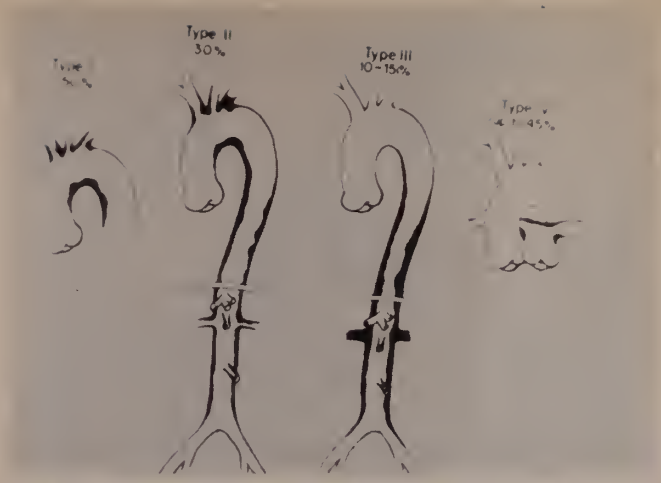

FIGURE 3. Patterns of arterial involvement in Takayasu's arteritis.

In this patient, the initial clinical features of the condition began many years before her first admission to the New York Hospital. At autopsy, we were unable to demonstrate any acute changes of Takayasu's arteritis. The evidence that remained was the presence of granulation tissue with plasma cells, lymphocytes, and occasional giant cells, together with destruction and replacement of the media of the blood vessels. In this chronic stage there are few if any inflammatory changes. There may be massive intimal hyperplasia, which is a secondary phenomenon, and variable degrees of elastic tissue damage—changes that can also be found in the more acute phase of the illness. In addition, in this condition adventitial fibrosis is quite common.[5]

Of the various arteritides, Takayasu's disease is unique in its tendency to cause aneurysm formation, in addition to arterial dilation and stenosis. When present, the stenosis identifies the disease for the pathologist. Of the general types of distribution of Takayasu's arteritis (Fig 3), the classic Type I involves the aortic arch. Our patient had Type II in which the entire root of the aorta is involved including the major branches of the arch and extending further in a caudal direction. Type III involves the descending thoracic and the abdominal segments of the aorta. The aorta is affected in 95% of patients, the subclavian arteries in 90%, the carotids in 81%, and the pulmonary arteries in nearly 60%.

Severe vascular involvement was evident in the aorta and its major branches in this patient. A cross-section of the right subclavian artery, 3 cm from it origin, secured at autopsy, shows marked dilation, together with atherosclerosis, which was no doubt a sequela of the original inflammation (Fig 4). As Dr Paget mentioned, any previously damaged

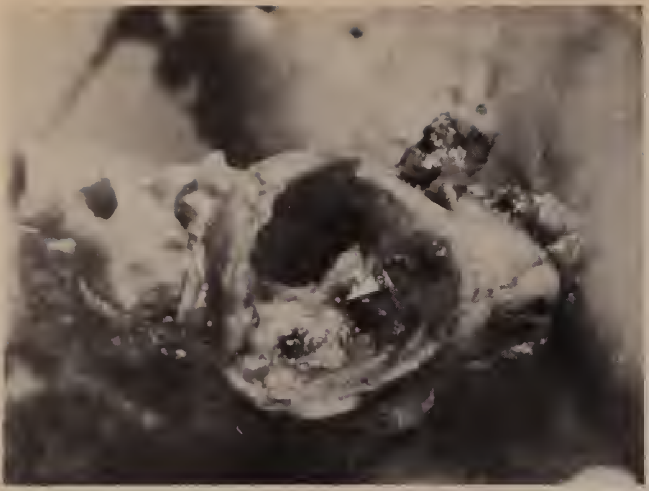

FIGURE 4. Secondary atherosclerosis (arrow) of markedly dilated right subclavian artery seen in cross section 3 cm from origin.

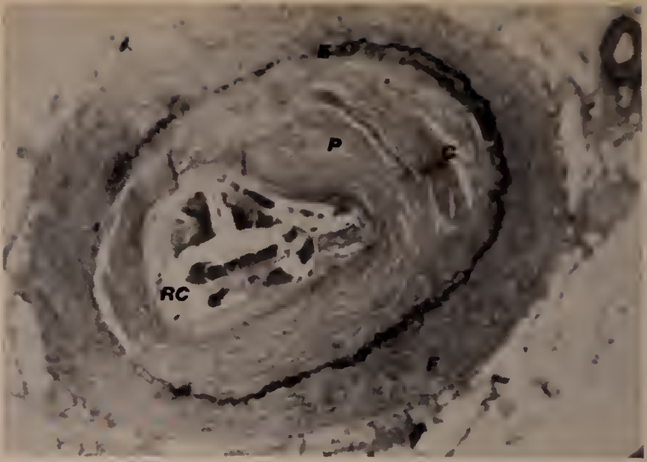

FIGURE 5. Healed mesenteric arteritis, with marked medial and adventitial fibrosis (F) and fragmented elastic lamina (E). Lumen is site of large atheromatous plaque (P) with cholesterol-crystal clefts (C) and recanalization (RC). (Verhoeff-van Gieson stain, original magnification × 25)

vessel has an increased susceptibility to atherosclerosis, and this young woman, while still under 30 years of age, certainly had considerable evidence of secondary atherosclerosis. She had not developed any wrinkling or "tree-barking" of the aorta, such as is seen in tertiary syphilis. The right renal artery, at a point 2.5 cm from its origin, measured 2 cm in diameter, which is approximately 6 to 7 times the normal caliber of that vessel; in addition, it too showed evidence of secondary atherosclerosis. Distal segments of the mesenteric arteries showed evidence of healed vasculitis, with disruption and fragmentation of the elastic lamina, proliferation of the intima, some adventitial fibrosis, and secondary atherosclerosis (Fig 5).

At autopsy the immediate cause of death was apparent when the abdomen was opened. Large volumes of blood were present in the abdomen and retroperitoneum. The hemorrhage had been due to rupture of the aneurysm at the proximal anastomosis of the aorta to the previously inserted aorto-iliac graft. The dilated aorta was thinned throughout, with focal calcification. On the day of death, at emergency laparotomy, the surgeons had inserted a 12-cm long synthetic graft between the descending thoracic aorta and the previously inserted aorto-iliac graft, but to no avail.

In the lung there was granuloma formation with numerous giant cells and caseation necrosis (Fig 6), but no evidence of Wegener's granulomatosis or of arteritis despite a careful search through numerous histologic sections. Consequently, I would have to interpret the original lung biopsy in one of two ways: either tuberculosis was present at that time, or Takayasu's arteritis was the condition seen. However, the latter seems highly unlikely in the absence of any arteritis in the major pulmonary arteries at autopsy. My choice, therefore, would be in favor of tuberculosis. Supporting that conclusion was the finding at autopsy of tuberculosis throughout the lungs, not only with the caseating granulomas, but with demonstration of acid-fact bacilli in lung tissue and in pulmonary hilar and retroperitoneal lymph nodes, as well as in one of the ovaries and in the retroperitoneum.

At the time of the resection of the left kidney, histologic sections showed only chronic interstitial nephritis and changes compatible with ischemia. There was no evidence of active arteritis. The left adrenal gland had also been removed and a diffuse infiltration with an eosinophilic amorphous acellular substance was found which stained positively with Congo red and was negative for birefringent amyloid. The type of amyloidosis seen in this patient is a secondary response to many forms of chronic inflammation. At autopsy it was no surprise then to find the spleen enlarged, weighing 440 g and showing amyloidosis. The liver was nearly twice normal weight and was almost completely replaced by amyloid.

In summary, this young woman developed Takayasu's arteritis at about age 16. After some time, she developed pulmonary and eventually miliary tuberculosis, with systemic amyloidosis as a secondary complication. The cause of death was a ruptured portion of the Dacron graft at a suture line 4 cm below the level of the renal arteries.

Dr Fuchs: Tuberculosis is by no means a frequent cause of a patient's death these days, certainly in this hospital; but we must keep it in mind, since it is a readily treatable condition.

David A. Silbersweig (Medical Student): Dr Paget, had you considered some form of allergic vasculitis in this patient?

Dr Paget: Most of the advanced arteritides with which we deal—Wegener's granulomatosis, allergic granulomatosis, Churg-Strauss disease—are acute illnesses. In this patient we were dealing with a disease that extended its course from age 16 to 31, more in keeping with a chronic process than with an acute one. Wegener's granulomatosis may go unrecognized in a patient for three to four years; but eventually that patient will require continued medical care because of the acute manifestations of the disease, and will die within a year, even while on steroid therapy, if not given appropriate chemotherapy. Churg-Strauss disease is a granulomatous disease that tends to be associated with asthma, eosinophilia and a form of polyarteritis nodosa in the organs involved, and tends to be a more acute disease process than we saw in this patient.

Howard M. Likier (Medical Student): Dr Paget, could you review again the indications for the nephrectomy in this case? Would angioplasty have been a good alternative

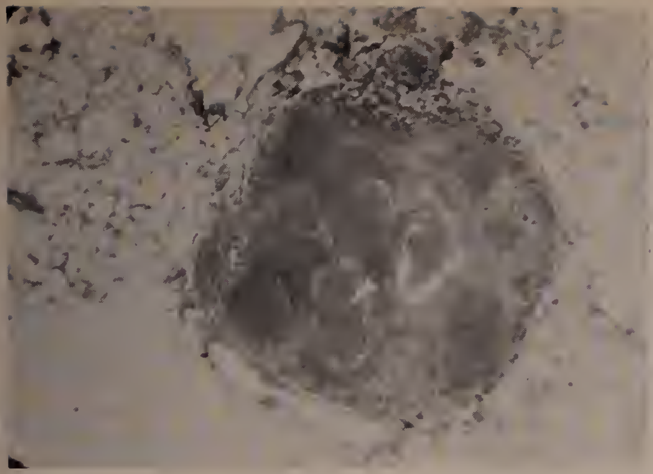

FIGURE 6. Pulmonary granuloma (arrow) with caseation necrosis and epithelioid giant cells. (Hematoxylin and eosin stain, original magnification × 25)

procedure?

Dr Paget: I can only speculate as to what clinical factors indicated the need for nephrectomy at that time. Renovascular stenosis as a cause of hypertension can be suspected if the renin level in the venous blood from the affected kidney is 1.5 or more times that of the venous renin level from the unaffected kidney or from the vena cava below the level of the renal veins. Hypertension attributable to renal artery stenosis can be resistant to drugs that reduce angiotensin levels such as captopril or saralasin, and it therefore may require a surgical procedure such as dilation of the stenosis by a renal artery angioplasty procedure or nephrectomy.

Dr Fuchs: Historically, the oldest procedure performed for such refractory renovascular hypertension was nephrectomy. Later procedures included renal artery arterectomy or a bypass, but these were technically difficult. The most common procedure today is renal artery angioplasty, with dilation of the stenosed segment by means of a balloon on the tip of an intravascular catheter. It would seem that this procedure might have been considered in this patient, who was known to have diffuse, severe vascular disease with both dilations and stenoses. It is likely that her physicians were concerned that the angioplasty might result in too great a degree of distention of the diseased vessel, with the threat of possible rupture. Though nephrectomy for refractory hypertension is performed infrequently these days, it was probably considered the safer and more appropriate treatment of choice in her case.

Dr Paget: During the nephrectomy, I wonder if the surgeons might not have had the chance to observe some evidence of the tuberculosis.

Dr Peterson: It would seem possible, since the retroperitoneal area was heavily seeded with acid-fast bacilli, as were the periaortic lymph nodes; but she had been on antituberculous therapy. Also, the surgeon is not usually thinking of other conditions, such as an infection, when his attention is absorbed by the technical aspects of the surgical procedure. When the specimen reaches the surgical pathology laboratory, it is probably already contaminated by other bacteria and the usual bacterial cultures are not helpful. In addition, to isolate acid-fast bacilli from such specimens, you must prepare special cultures.

Dr Fuchs: Keep in mind that the nephrectomy was performed three months before she died. At that time the tuberculosis might well have been less evident. Also, during the three-month interval between the nephrectomy and her death, she continued on the steroid therapy.

FINAL DIAGNOSES

Takayasu's arteritis, healed, with secondary atherosclerotic changes and terminal rupture of the abdominal aorta.

Disseminated *Mycobacterium tuberculosis*, involving the lungs, lymph nodes, retroperitoneum, and an ovary.

Systemic amyloidosis, secondary to tuberculosis.

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—Editor

At its annual meeting, the House of Delegates of the Medical Society of the State of New York adopted the following resolution:

That the Medical Society of the State of New York recommend that steps be taken toward the goal of total prohibition of the sport of boxing.

Autonomous thyroid nodule with intermittent excess hormonogenesis

Jean-Robert Leonidas, MD, George C. Schussler, MD

Unlike Graves' disease, an autoimmune disorder with exacerbations and remissions, hyperthyroidism caused by a single toxic adenoma of the thyroid gland (Plummer's disease) is usually unremitting, unless the gland is altered by treatment or a spontaneous intranodular hemorrhage. We describe a patient with an untreated autonomous thyroid nodule with intermittent excess hormonogenesis that could not be explained by structural changes in the nodule. Major reviews of autonomous thyroid nodules have not reported this phenomenon.[1–5]

Case Report

A 65-year-old woman was treated at the thyroid clinic of the Kings County Hospital for eight years. She was referred by the clinic because of a 4-cm nodule in the left lobe of the thyroid gland. Despite a borderline low serum T_4 concentration (Table I) the patient's metabolic status was unremarkable. The serum thyroid stimulating hormone level was within normal limits. A radioactive iodine uptake of 11% was limited to the left lobe; the right lobe was visualized on a technetium scan and on a radioiodine scintigram after stimulation with thyrotropin. The patient was tested two to three times a year with serial thyroid hormone level studies. Two years after the original referral, elevated T_4, T_3, and T_3RU levels were obtained; however, these were not noted until her next visit. On physical examination the patient's metabolic status appeared normal. She had lost 14 lb and her pulse rate was 96 beats/min. The patient had visited a private medical doctor during the six-month interval between her clinic appointments for treatment of tiredness and nervousness. At that time an elevated serum T_4 determination was again obtained. However, when the patient returned to the clinic three months later, her serum T_4, T_3, and T_3RU values were within normal limits. The patient's metabolic status was stable for the next few years.

Three years after elevated hormone levels were first discovered, she again became thyrotoxic. A thyrotropin releasing hormone stimulation test showed no significant thyroid stimulating hormone response, but there was a small rise in the total triiodothyronine level (250, 259, and 292 ng/dL at 0, 30 and 60 minutes, respectively). A thyroid stimulating hormone stimulation test showed a progressive rise in both T_4 and T_3 levels over a three-day period (Table I). Antibodies to thyroid hormone were absent. The patient refused radioiodine treatment and was started on propylthiouracil therapy, 600 mg daily. Four months later her metabolic status had stabilized and propylthiouracil therapy was tapered to a maintenance dose of 100 mg daily.

Discussion

The abnormal thyroid function values obtained in the hospital clinic and in the private doctor's office, as well as the patient's symptoms and the concomitant 14-lb weight loss at the time of the initial elevated T_4 level leave no doubt that the patient was thyrotoxic at that time. There was no evidence of ingestion of thyroid hormone or of exposure to iodine. Transient hyperthyroidism in autonomous nodules has been described in association with acute hemorrhagic infarction,[6] but this patient did not have pain or tenderness, and a repeat radioiodine scan after the patient became toxic demonstrated the same pattern of activity localized to the left lobe as had been seen initially (Fig 1).

Although autonomous thyroid nodules are by definition not dependent on thyroid stimulating hormone, there is evidence that they retain the hormone receptors and may be hypersensitive to exogenous thyroid stimulating hormone.[2,7] It is conceivable that the suppressed thyroid stimulating hormone levels in these patients may result in an increased number of receptors. The in-

TABLE I. Serial Thyroid Function Values

Date	T_4 (μg/dL)	T_3RU (%)	T_3 radioimmunoassay (ng/dL)	Weight (lb)
9/70	4.4	28	—	201
2/77	9.2	26	210	199
4/77	8.7	27	210	200
9/77	6.8	29	200	199
6/78*	16	38	700	185
9/78**	14.5	—	—	187
12/78	10.4	31	220	192
8/79	10.2	32	220	195
9/80	10.6	30	210	198
10/81*	16.2	40	—	190
baseline	12.9	35	275	—
day 1†	14.9	39	337	—
day 2†	17	41	363	—
day 3†	14.5	42	372	—

* Elevated values in hospital clinic.
** Elevated T_4 level in doctor's office.
† Immediate T_4 and T_3 response to thyroid stimulating hormone stimulation, 10 units daily for three days.

From the Department of Medicine, SUNY-Downstate Medical Center, Brooklyn, New York.

Address correspondence to Dr Leonidas, 967 Ocean Avenue, Brooklyn, NY 11226.

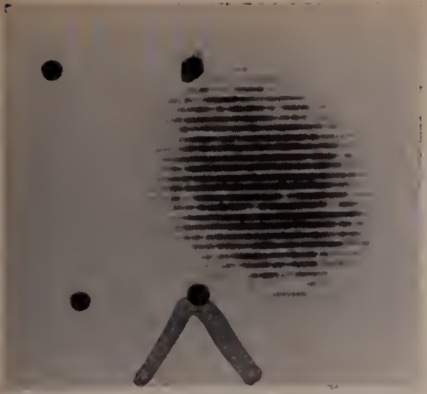

FIGURE 1. ^{131}I scan obtained after thyrotoxicosis recurred. The ^{131}I uptake is 47% and is localized to the nodule in the left lobe.

crease of serum T$_4$ and T$_3$ levels the day after the first of the three injections with thyroid stimulating hormone may reflect such a response by the nodule, since the suppressed lobe would be unlikely to have a sufficient store of hormone to respond in such a rapid way.

Few patients with autonomous nodules become thyrotoxic, and when the nodules do become toxic, they may revert to a lower level of secretion. Both these observations seem to be explained by the tendency of autonomous nodules to undergo spontaneous central degeneration.[1,3] This explanation is consistent with the lack of reports of recurrent cycles of toxicity in autonomous nodules, similar to those that occur in Graves' disease.

It is unlikely that this patient had a variant of Graves' disease because of the suppressed activity of the right lobe and the response to thyroid stimulating hormone. This patient had not only spontaneous regression of excess hormonogenesis, but also a later recurrence of the toxic state. This cyclical pattern is suggestive of functional changes within the nodule rather than a destructive process limiting hormonogenesis. The absence of pain and the continued localization of ^{131}I uptake in the nodule when the patient became thyrotoxic rule out the possibility of transient thyrotoxicosis associated with acute hemorrhagic infarction. Spontaneous improvement of thyrotoxicosis due to a single autonomous nodule does not preclude a subsequent recurrence of thyrotoxicosis, although a review of the literature suggests that this sequence is exceedingly rare.

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See also p 537.

Ovarian vein thrombosis mimicking ectopic pregnancy

AKINORI ADACHI, MD, JOSEPH SEGEN, MD, JOHN K. H. LI, MD

The diagnosis and management of abdominal pain in women of childbearing age center on a group of disorders that is unique to this population. Among this group are puerperal or postabortal ovarian vein thrombosis and thrombophlebitis.

We report on a young woman with ovarian vein thrombosis who was suspected of having an ectopic pregnancy.

CASE REPORT

A 25-year-old woman with a regular, 28-day menstruation cycle that lasted three days was admitted on September 24, 1982 to North Central Bronx Hospital because of increasing sharp pain in the right lower quadrant of two days' duration and amenorrhea of 14 weeks' duration. The patient had had one day of vaginal bleeding three weeks prior to admission. She was para 3-0-1-3. She underwent an exploratory laparotomy in 1975 for an ectopic pregnancy. She had used an intrauterine contraceptive device (IUD) for 16 months prior to this admission.

On physical examination the abdomen was soft and flat. There was a low midline scar, good bowel sounds, tenderness to deep palpation, and muscle guarding in the right lower quadrant. On pelvic examination there was minimal yellowish discharge in the vagina. The cervix was multiparous and was not tender. An IUD string was present. The uterus was 6 cm long and in an axial position. The left adnexa were unremarkable, but the right were tender without an appreciable mass. Rectal examination confirmed these findings. Results of a culdocentesis were within normal limits. A urinary pregnancy test was negative. Gram's stain of a cervical smear was negative for intracellular diplococci. Other laboratory data were within normal limits.

On September 27th she was examined under general anesthesia because of persistent pain in the right lower quadrant. An ill-defined right adnexal mass was palpated. A clinical diagnosis of ectopic pregnancy was made based on the following: a pelvic mass, persistent pain without clinical or laboratory evidence of pelvic inflammatory disease, amenorrhea of 14 weeks' duration with a previous history of regular menstruation, and a previous ectopic pregnancy. Immediately following a suction dilatation and curettage, which yielded minimal tissue, an exploratory laparotomy was performed without laparoscopy. The uterus, the left fallopian tube, and both ovaries appeared normal. Both the left and right ovarian veins were dilated; in addition, multiple small, firm thrombi were palpated in the ovarian veins in the right infundibulopelvic ligament. These segments of veins were removed, starting half a centimeter cephalad to the thrombi. The distal half of the right fallopian tube was also removed.

From the Departments of Obstetrics and Gynecology (Dr Adachi), and Pathology (Drs Segen and Li), Montefiore-North Central Bronx Hospital, Albert Einstein College of Medicine, Bronx, New York.

Address correspondence to Dr Adachi, Head of Gynecology, Department of Obstetrics and Gynecology, North Central Bronx Hospital, 3424 Kossuth Ave, Bronx, NY 10467.

The patient received subcutaneous mini-heparin therapy (5,000 units, every 12 hours) for six days, starting from the first day after surgery. She was discharged on the seventh day after surgery.

Examination of the uterine tissue showed proliferative endometrium and pieces of hyalinized tissue. The specimen containing the ovarian veins measured 3 × 2 × 1 cm (Fig 1). Within this specimen were several veins that measured from 0.3 to 0.6 cm in diameter, all of which were distended with thrombotic material. Microscopic examination showed the thrombi to be undergoing the process of organization, including fibroblastic and capillary ingrowth, deposition of collagen, and endothelial growth over them. No inflammatory reaction was present in any tissue examined (Fig 2).

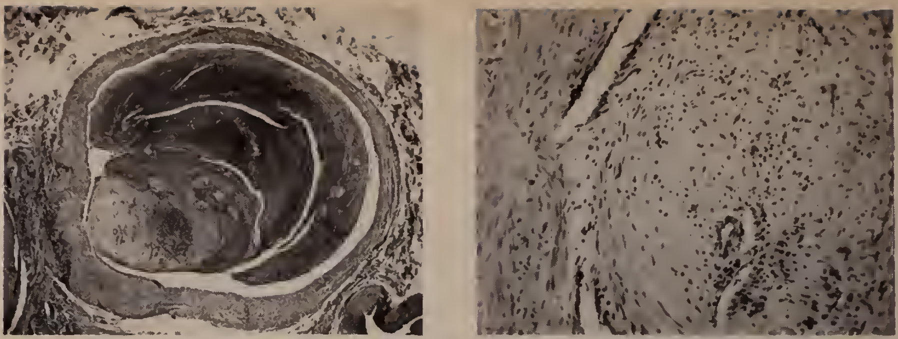

FIGURE 2. Left, a vein distended by layers of older (paler) and fresher (darker) thrombus material. The cracks in the thrombus are artifacts of tissue processing. (Hematoxylin & eosin stain, original magnification ×15); Right, detail of the older part of the thrombus, showing its attachment to endothelium of vessel wall (left), and granulation tissue in the thrombus. Note absence of inflammatory cells in the vessel wall. (Hematoxylin & eosin stain, original magnification ×100)

DISCUSSION

The venous thrombi were judged to have developed between one and two weeks previously. In addition, there were thrombi of a few days' duration layered over the older ones, with the combination resulting in complete occlusion of the veins. The findings of hyalinizing decidual tissue in the uterine sample and organizing thrombi in the ovarian veins indicate an event that had probably started several weeks prior to laparotomy. Based on the pathologic findings and the bleeding that occurred three weeks prior to admission, we speculated that a spontaneous abortion had occurred, although beta-human chorionic gonadotropin level determined by radioimmunoassay on September 26 was less than 4 mU/mL.

Ovarian vein thrombotic disease is most frequently seen in the postpartum period, commonly on the second and third days after delivery[1] and rarely in the postabortal period.[2] The literature supports the view that endometritis causes bacterial phlebitis with intimal damage and subsequent formation of infected thrombi.[3] However, endometritis was suspected or proven in only 5 to 45% of cases.[1] If this patient had had an infection, it had already subsided.

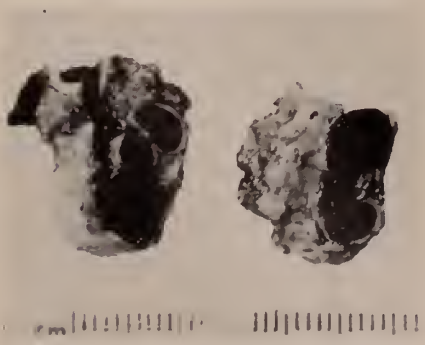

FIGURE 1. Gross appearance of thrombosed ovarian veins. Millimeter scale at bottom.

In 1971, Brown and Munsick[1] refocused attention on puerperal ovarian vein thrombophlebitis and pointed to the characteristic findings of fever, lower abdominal pain, and a rope-like, tender mass in the abdomen. Ovarian vein thrombotic disease can mimic ectopic pregnancy, acute appendicitis, a twisted ovarian cyst, torsion of the ovary, pyosalpinx, hematoma of the broad ligament, a degenerating fibroid, volvulus of the intestines, perinephric or subdiaphragmatic abscess, or cellulitis.[1,4] Whereas laparoscopy has gained in popularity in the diagnosis of ectopic pregnancy, we believe that the lateral location and relative inaccessibility of the ovarian veins place distinct limits on the value of this procedure in providing a visual identification of ovarian vein thrombosis. It is possible that some patients with "negative laparoscopy" may have had ovarian vein thrombosis.

Clarke-Pearson and associates[5] stated that the diagnostic standard for pelvic vein thrombosis is ascending contrast venography, but the only diagnostic method available to evaluate the internal iliac venous system is retrograde venography. However, venography is not often performed because it is painful to the patient and involves the risk of dislodging a thrombus.[5] Wilson and Lerner[6] demonstrated a tubular anechoic structure of an ovarian vein thrombophlebitis in a woman following parturition, although the proper interpretation of the sonographic findings was made after surgery. They found an area of ring enhancement in the same patient using computed tomography (CT). Their conclusion was that, in the appropriate situation, both CT scans and sonography are useful in identifying ovarian vein thrombophlebitis without surgery.[6]

When ovarian vein thrombotic disease is suspected, treatment with antibiotics and anticoagulants has been advocated by Munsick and Gillander.[3] Failure to respond to medication in four to five days or occurrence of pulmonary embolism warrants surgical intervention.[1,3,7]

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See also p 542.

Congenital pulmonary arteriovenous malformations

S. K. Kim, MD, Jose galindo, MD, Arthur Riordan, MD, Ronald K. H. Chang, MD

Congenital pulmonary arteriovenous fistula is a malformation of the pulmonary vessels caused by abnormalities of capillary development.[1] Congenital arteriovenous fistulas are associated with hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome) in 50 to 60% of patients.[2] The presence of an arteriovenous fistula in the pulmonary circulation results in a right to left shunt with arterial oxygen desaturation. This report describes a case of congenital pulmonary arteriovenous fistula that was successfully treated with surgery.

Case Report

A 17-year-old woman was admitted on September 19, 1983 for evaluation of a lesion in the lower lobe of the left lung. She was in excellent physical condition except for mild dyspnea on exertion. She had had two episodes of acute bronchitis and mild bronchial asthma of nine months' duration. She was treated with theophylline and an antibiotic on each occasion.

Chest films taken nine months prior to admission, during her first episode of bronchitis, revealed an abnormality in the lower lobe of the left lung that was interpreted as being pneumonia. Seven months prior to admission she had a second episode of bronchitis. A repeat chest roentgenogram was taken and showed a lesion in the lower lobe of the left lung. Five months prior to admission a chest roentgenogram confirmed the presence of a lesion in the lower lobe of the left lung (Fig 1).

A computerized tomographic (CT) scan of the chest with contrast revealed an area of increased density in the lower lobe of the left lung. This was interpreted as an arteriovenous malformation with large vessels extending into the mass from the hilus (Fig 2). On August 25, 1983, a linear tomographic scan also showed the lung mass with large vessels entering it. Intravenous angiography using 15 μl of sodium pertechnitate identified the large arteriovenous shunt in the lower lobe of the left lung. On admission, the results of laboratory studies were as follows: hemoglobin, 17.1 g/dL; hematocrit, 53%; and white blood cell count, 10,700/mm^3. Chemistry studies and pulmonary function tests were within normal limits. Blood gas test results were pH, 7.49; P_{CO_2}, 27 mm Hg; P_{O_2}, 77 mm Hg; S_{AO_2}, 95.8%; HCO_3, 20 mEq/L; base excess, 0. An electrocardiogram was unremarkable. An exploratory thoracotomy of the left side of the chest and segmental resection of the anterior medial segment of the lower lobe of the left lung were performed (Fig 3). The pathology report showed the arteriovenous malformation in a pulmonary tissue segment (Fig 4). The patient's postoperative course was uneventful, and she was discharged from the hospital nine days after surgery.

Discussion

In 1897 pulmonary arteriovenous fistulas were first described by Churton, a pathologist in London.[3] In 1940, Shenstone performed the first operation, a pneumonectomy, for this disorder.[4] Between 1952 and 1973, 36 of 63 patients at the Mayo Clinic with pulmonary arteriovenous fistula underwent surgery.[5] Terry et al[6] used selective miniballoon occlusion for the non-surgical elimination of multiple pulmonary arteriovenous fistulas in 1980.

Pulmonary arteriovenous fistulas are usually congenital but can be acquired later in life. Acquired pulmonary arteriovenous fistulas are rare and can be caused by metastatic thyroid carcinoma, cirrhosis of the liver, pulmonary schistosomiasis, and penetrating lung trauma.[7,8]

FIGURE 1. Chest roentgenogram showing lesion in lower lobe of left lung (arrow).

Congenital pulmonary arteriovenous fistula is also rare and is sometimes associated with hereditary hemorrhagic telangiectasia.

Utzon and Brandrup[9] described three forms of pulmonary arteriovenous malformation. The first is solitary or may consist of several isolated arteriovenous fistulas. The second is a form with multiple fistulas. The third has many telangiectatic anastomoses, widespread in both lungs. The case described may belong to the first form, since the solitary lesion involved only the anteromedial basal segment of the lower lobe of the left lung.

An arteriovenous fistula may produce a right to left shunt without the occurrence of gas exchange. Chronic hypoxia stimulates erythropoiesis, producing secondary polycythemia. Neurologic symptoms and signs can occur due to cerebrovascular thrombosis asssociated with polycythemia. A large right to left intrapulmonary shunt can produce emboli or allow paradoxical emboli to develop. Emboli may result in cerebrovascular accidents and, if septic, may form a brain abscess. Spontaneous hemothorax and massive hemoptysis can also occur as complications. Epistaxis can occur, but is usually associated with hereditary hemorrhagic telangiectasia. Bacterial endocarditis has also been reported as a complication. Dyspnea and epistaxis were the two most frequent symptoms described, but Dines and

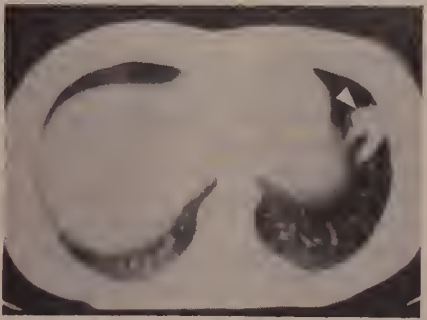

FIGURE 2. Computerized tomographic scan of the chest with contrast shows an arteriovenous malformation (arrow).

From the Departments of Surgery, Tri-County Memorial Hospital, (Drs Kim, Galindo, and Chang), Gowanda, NY, and Our Lady of Victory Hospital (Dr Riordan), Lackawanna, NY.

Address correspondence to Dr Kim, 6878 Erie Road, Derby, NY 14047.

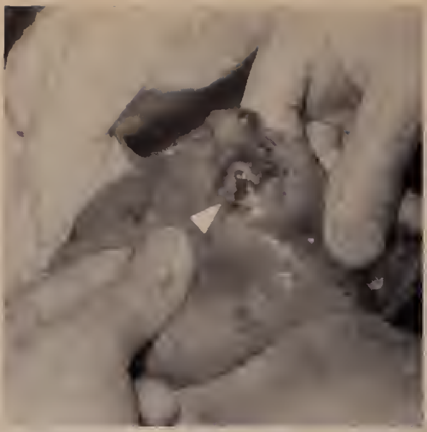
FIGURE 3. Pulsating arteriovenous fistula (arrow) at anterior basal segment of lower lobe of left lung.

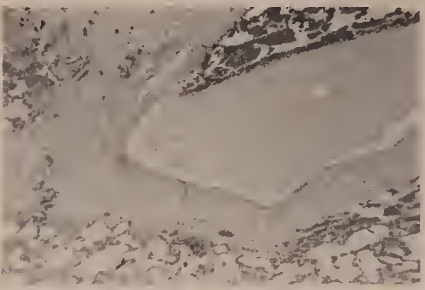
FIGURE 4. Photomicrograph of arteriovenous fistula (arrow).

colleagues[10] reported that 26% of patients had no pulmonary symptoms and 13% were asymptomatic.

This patient did not have the symptoms and signs of arteriovenous fistula except for dyspnea on exertion. The lesion was discovered serendipitously on chest films taken for acute bronchitis. The patient's mother and sister have bronchial asthma, but there is no history of hereditary hemorrhagic telangiectasia. In this instance it was deemed appropriate to carry out surgical extirpation of the lesion to prevent potential complications.

A patient with pulmonary arteriovenous fistula should be asked for a complete history and should undergo a physical examination to rule out hereditary hemorrhagic telangiectasia. A chest roentgenogram plays an important role in the diagnosis. The most common findings are single or multiple nodules, most often in a lower lobe. Tomography can help in elucidating the feeding arteries and draining veins. A CT scan of the chest with and without intravenous contrast material, and radionuclide angiography with sodium pertechnitate or other suitable blood pool tag can also demonstrate pulmonary arteriovenous fistulas located peripherally, especially when behind the heart. Angiography is not only important to determine the size and number of fistulas, but also to differentiate the pulmonary and systemic blood supply.[11] Blood gas measurements should be checked to determine the severity of hypoxia due to right to left shunting. Contrast echocardiography with indocyanine green dye can detect even minor right to left shunting.[12] The measurement of differential pulmonary venous oxygen content at catheterization may be necessary to evaluate the severity of the capillary defect.

Segmental resections and lobectomy for pulmonary arteriovenous fistula have been used in the past, but for smaller lesions wedge resection can be employed. A pneumonectomy should be avoided because of the possibility of undetected lesions in the contralateral lung. Recent literature cites occlusion as an alternative therapy for multiple pulmonary arteriovenous fistulas.[6] If the resection of the fistula is complete, there is little chance that new fistulas will develop.

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See also p 539.

Respiratory failure in amyotrophic lateral sclerosis

MICHAEL DARAS, MD, ALFRED J. SPIRO, MD, MICHAEL SWERDLOW, MD

Patients with amyotrophic lateral sclerosis (ALS) are known to have respiratory compromise, but this usually occurs late in the course of the disease. Few cases of ALS have been reported in which respiratory problems such as exertional dyspnea[1,2] or acute respiratory failure[3-6] constituted the major symptoms. We report two additional cases of ALS in which the patients experienced severe dyspnea but no significant weakness.

CASE REPORTS

Case 1. A 60-year-old man presented with dyspnea on exertion for four months' duration. In the two weeks before his admission he had three episodes of respiratory failure, with the last one resulting in coma with abnormal arterial blood gas levels: pH, 7.06; Pa_{CO_2}, 77.5 mm Hg; Pa_{O_2}, 68 mm Hg. After respiratory assistance with a volume control respirator (Bennet MA-1), he regained consciousness and his blood gas levels improved: pH, 7.54; Pa_{CO_2}, 23 mm Hg; Pa_{O_2} 92.4 mm Hg).

On examination, he had minimal muscle weakness. The reflexes were brisk, but plantar responses were flexor. Fasciculations were

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From The Departments of Neurology, The Albert Einstein College of Medicine (Drs Daras and Spiro), the Montefiore Hospital and Medical Center (Dr Swerdlow), Bronx, New York.

Address correspondence to Dr Daras, Associate Director, Department of Neurology, New York Medical College, Lincoln Medical and Mental Health Center, 234 East 149th St, Bronx, NY 10451.

TABLE I. Patients in Reported Cases of ALS Presenting with Respiratory Insufficiency

Case No.	Source	Age	Sex	Duration of Dyspnea	Neurologic Findings	Diaphragmatic Involvement
1	Miller et al[1]	66	M	17 months	Wasting of hand muscles	+
2		71	M	9 months	Wasting of hand muscles, left Babinski	+
3		49	M	24 months	Wasting of muscles of the thoracic wall & pelvic girdle	+
4	Paul et al[2]	60	M	11 weeks	Wasting of left hand muscles	−
5	Fromm et al[3]	68	M	3 months	Wasting of hand muscles	+
6		69	M	2 weeks	Generalized fasciculations	+
7	Parhad et al[4]	68	F	3 months	Dysarthria, mild generalized weakness	+
8		46	F	acute onset	Nasal speech, generalized muscle atrophy	+
9	Sivak et al[5]	57	M	3 months	Slight distal weakness, fasciculations, left Babinski	+
10	Nightingale et al[6]	55	M	10 months	Fasciculations, slight weakness	+
11		65	M	—	Fasciculations, proximal weakness	−
12		63	M	—	Fasciculations	−
13	Present cases	60	M	4 months	Generalized fasciculations	+
14		59	M	3 months	Mild generalized weakness, bilateral Babinski	+

present in several muscles but did not involve the tongue. Blood tests, including those for muscle enzymes, were within normal limits. Chest fluoroscopy revealed paralysis of the left hemidiaphragm. Maximum inspiratory and expiratory pressures were −16 cm and +32 cm water, respectively. A Tensilon test result was negative. Motor nerve conduction velocities were normal. Electromyography showed multiple fibrillations at rest, frequent fasciculations, and high voltage long-duration polyphasic action potentials that supported the clinical diagnosis of ALS. The patient has remained dependent on the respirator since his admission.

Case 2. A 59-year-old man presented with dyspnea, wheezing and a 40-lb weight loss for three months. One week prior to his admission, dyspnea worsened, and he became confused and disoriented.

On admission the patient was lethargic and in severe respiratory distress. The arterial blood gas examination showed pH, 7.35; $PaCO_2$, 90 mm Hg; PaO_2, 57 mm Hg. After respiratory assistance with a volume control respirator (Bennet MA-1), his mental status improved, and arterial blood gas levels returned to normal. The neurologic examination revealed tongue atrophy but no fasciculations. There was minimal muscle weakness. The tendon reflexes were brisk and plantar responses extensor. Occasional fasciculations were present in several muscles. A Tensilon test result was negative. Blood test results including muscle enzymes were normal. A spinal fluid examination showed no cells, total protein of 28 mg% and glucose, 67 mg%. Chest fluoroscopy revealed paralysis of the diaphragm. Maximum inspiratory and expiratory pressures were −9 cm and +30 cm water, respectively. Nerve conduction velocities were normal. Electromyography showed fibrillations and positive sharp waves at rest, frequent fasciculations, and high voltage polyphasic potentials that supported the diagnosis of ALS. This patient has also remained dependent on a respirator.

DISCUSSION

The two patients were admitted with respiratory compromise; the dyspnea was initially attributed to other causes. The diagnosis of ALS was considered after respiratory failure developed and neurologic consultation was sought. Finally, electromyographic examination established the diagnosis.

Only rarely is ALS diagnosed on the basis of respiratory insufficiency. When the typical manifestations of the disease—muscle weakness and wasting, spasticity, hyperreflexia, and fasciculations—are absent or subtle, a diagnostic problem arises. Since the first report by Miller et al,[1] a total of 14 cases (including the present two) have been reported in the English literature in which the patients sought treatment for respiratory distress (Table I). In some patients the presenting symptom was acute respiratory failure, whereas in others it was a chronic exertional dyspnea for which, as in the present cases, no specific cause was found for several months. Only after other causes of respiratory failure had been excluded and more typical signs of the disease occurred was the diagnosis of ALS considered. Although diaphragmatic paralysis may suggest the possibility of ALS, other neurologic disorders such as myelopathies, neuropathies, and myopathies should be excluded.[5]

With few exceptions, the patients manifested diaphragmatic involvement. During quiet breathing, the intercostal muscles have sufficient compensatory power[7]; however, under conditions of exertion, dyspnea will occur. Involvement of both the diaphragm and the intercostal muscles will result in severe respiratory failure. The anterior horns of the cervical spinal column, which contain the phrenic nuclei, seem to be prominently and preferentially involved in the few cases studied at autopsy.[3,4,6] Although diaphragmatic paralysis may suggest the possibility of ALS, other neurologic disorders need to be excluded.[4]

Pulmonary function studies, such as lung volume and air flow analyses, in patients with respiratory muscle weakness reveal findings that have several similarities with those in chronic obstructive lung disease.[7] Since both conditions usually occur in the same age group and may occasionally coincide, it is important to differentiate them by measuring the strength of the respiratory muscles.

Goldstein et al[8] have suggested that maximum mid-inspiratory and mid-expiratory flow be used as a test to aid in the diagnosis of respiratory muscle weakness. A more reliable test to assess the strength of respiratory muscles might be the measurement of maximal static inspiratory and expiratory pressures. As Black and Hyatt[9] pointed out, these pressures remain normal in patients with obstructive lung disease. However, they can decrease early in the course of neuromuscular diseases, even when spirometric measurements are still within normal limits. Griggs et al[10] confirmed the validity of measuring maximal static inspiratory and expiratory pressures in order to evaluate the strength of the respiratory muscles. If the pressure levels are abnormal, even in the absence of any overt muscle weakness, a detailed neurologic examination is necessary. The presence of fasciculations, hyperreflexia, and extensor plantar responses may lead to the proper diagnosis, and electrodiagnostic studies may provide corroborative evidence. Respiratory support with a ventilator[5] may prolong the life of patients with ALS who are not yet completely disabled by the disease.

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Transient acquired factor X deficiency associated with pneumonia

MARK S. CURRIE, MD, ALFRED M. STEIN, MD, PRADIP K. RUSTAGI, MD,
ARLEEN N. BEHRENS, GERALD L. LOGUE, MD

Activation of factor X via the intrinsic or extrinsic coagulation cascade is requisite to normal coagulation; the lack of factor X results in overt bleeding manifestations. Isolated factor X deficiency may be hereditary (Stuart Prower disease) or acquired—especially in the setting of systemic amyloidosis.[1] The case described here, together with three other recent reports, illustrates the occurrence of a transient factor X deficiency as part of an acute illness with pulmonary involvement.

CASE REPORT

The patient was a 63-year-old man who had undergone thyroid surgery and an appendectomy in the past with no complications, and who had had no coagulation difficulty prior to his acute illness. After a week of malaise and skin soreness, the patient had night sweats, cough, and lung congestion. Chest films showed an infiltrate in the upper lobe of the right lung, and erythromycin therapy was initiated. Within three days, gross hematuria and subcutaneous hematomas developed which produced gross swelling and discoloration of the right thenar eminence, left forearm, and left hip and groin. Erythromycin therapy was discontinued.

On admission, prothrombin time and partial thromboplastin time were 27 and 47 seconds, respectively (normal, 12 ± 1 and 35 ± 5 seconds). Factor level assays showed greater than 80% activity of factors VII and V, but the factor X level was less than 10% in both the prothrombin time and partial thromboplastin time mode. The patient's prothrombin time was correctable in vitro by mixture with normal plasma (immediate and after 60 minutes at 37°C incubation) (Table I), but it was not correctable in vivo by the infusion of fresh frozen plasma. After the administration of 5 units of fresh frozen plasma over 24 hours, the prothrombin time was unchanged at 27 seconds. Ten milligrams of intravenous vitamin K, given on admission, was also without effect. The platelet count was 550,000/mm^3, and the bleeding time was normal. Results of other studies, including serum protein electrophoresis, quantitative immunoglobulins, blood chemistries, fibrinogen and fibrin degradation products, analysis of bone marrow aspirate and biopsy, liver and spleen scan, bone scan, intravenous pyelogram, bronchoscopy, and bronchography, were either within normal limits or consistent with a pulmonary infection. There was no clinical evidence of amyloidosis.

Gross hematuria began to clear within 24 hours of admission, and no new significant hematomas or other bleeding developed, suggesting that the patient was beginning to recover by the time of admission. As the patient's lung infiltrate cleared, the prothrombin time and partial thromboplastin time returned to normal, with a prothrombin time of 14 seconds after two weeks associated with a 40% factor X level, and a normal prothrombin time and factor X level one month later (Fig 1). Only normal respiratory flora were isolated from cultures, and acute and convalescent titers for adenovirus, legionella, and mycoplasma were not diagnostic (<1:16). Influenza B antibody by hemagglutination inhibition titer was 1:32 at the time of admission and was unchanged two weeks later (normal <1:16). Thus, this patient had pneumonia and transient, symptomatic factor X deficiency that could not be corrected by plasma infusion, suggesting a rapid in vivo consumption or clearance of factor X.

DISCUSSION

This report brings to seven the number of cases of transient acquired factor X deficiency described in the literature. There has been one report each of transient factor X deficiency due to methylbromide fungicide exposure,[2] and tumor-associated factor X deficiency[3] that remitted after removal of a 1-kg adrenal cortical tumor and a small renal cell primary tumor. A third instance of transient factor X deficiency was described in a seven-year-old boy; no clear prodrome or associated illness was described,[4] but laboratory test results and the spontaneous resolution were similar to those in the four other patients—including this one—that have been described.[5-7] These last four reports have all been associated with acute pulmonary disease. In the patient described by Peuscher et al[5] there was evidence of lobar pneumonia, but a subsequent rise in the mycoplasma complement fixation titer from 1:8 to 1:64 was seen. The patient reported by Edgin et al[6] was described as having a "viral syndrome" with bilateral pleural effusions, and the most recent case of Bayer and associates[7] was described as "viral pneumonia." In

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From the Buffalo General Hospital, Hematology Laboratory, State University of New York at Buffalo, Buffalo, New York.

Address correspondence to Dr Currie, Assistant Professor Department of Medicine, SUNY at Buffalo School of Medicine, 100 High St, Buffalo, NY 14203.

TABLE I. Clotting Times and Factor Assays*

	Prothrombin time, sec	Activated Partial Thromboplastin time, sec
Patient	23.6	39.3
Pooled control	10.6	24.0
1:1 mix		
immediate	13.3	29.0
1 hour incubation at 37°C	13.1	—
1/10 dilution with factor X deficient plasma		
Patient	35	65
Control	20	48
1/20 dilution with factor X deficient plasma		
Patient	38	73
Control	23	53

* Routine prothrombin time and partial thromboplastin time determined on a Coagulyzer (Sherwood). Factor assays were carried out by manual waterbath technique using Autosimplastin and Auto-APTT (General Diagnostics) for the prothrombin time and partial thromboplastin time modes, respectively.

the patient presented here, systemic symptoms preceded the development of pulmonary symptoms, but a specific infectious agent was not identified. Erythromycin had been given to this patient, whereas in two of the other reported cases the patients had received penicillin derivatives.[5,7] Thus, although no specific etiologic agent is certain, the clinical course of the coagulopathy and the laboratory findings have been remarkably similar: an acute illness with symptomatic intramuscular, subcutaneous, and mucosal bleeding unresponsive to vitamin K_1 or factor X infusion, but resolving spontaneously over two to four weeks time.

Most coagulation factor "inhibitors" are demonstrable by plasma mixing experiments. Such studies on this patient's plasma failed to demonstrate the presence of such an inhibitor, and no circulating inhibitor has been found in the other reports of isolated acquired factor X deficiency. Similarity to amyloid-related factor X deficiency has been recognized[5,6] and includes substantial in vitro correction by mixture with normal plasma (unaffected by incubation) and inability to correct the coagulation defect with fresh frozen plasma or other factor X-containing preparations in vivo.

The apparent mechanism is rapid clearance of infused factor X. Studies in patients with amyloid and acquired factor X deficiency have suggested rapid binding of factor X to amyloid-related protein and diffuse deposition within the vasculature with concentration in the liver and spleen.[1] It is not clear whether factor X binds to amyloid deposits in situ, or binds to a circulating paraprotein, forming a complex that is rapidly cleared. In transient acquired factor X deficiency the mechanism of rapid factor X disappearance may be similar, but lack of a complete understanding of the pathophysiology in the amyloid-related cases makes comparison speculative. Peuscher et al[5] were unable to detect immunoglobulin (Ig) G antibodies to factor X in a patient with pneumonia-associated factor X deficiency. The possibility of an IgM antibody—perhaps more consistent with the three-week time course in these patients—has not been studied in any of the cases described. Other possibilities include an effect on factor X by a viral or bacterial product, either by binding or enzymatic alteration of factor X, an unusual interaction between factor X and an "acute phase reactant," or some combination of these factors causing rapid clearance of factor X in the reticuloendothelial system or vasculature.

Calling attention to the syndrome of transient acquired factor X deficiency associated with pneumonia may facilitate recognition of similar occurrences, so that precipitating factors and pathophysiologic features may be further investigated.

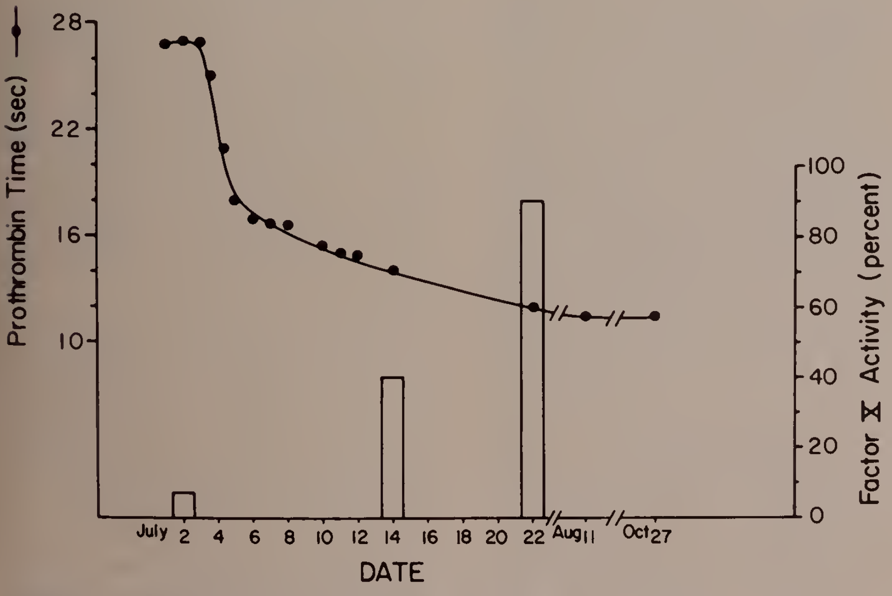

FIGURE 1. Time course of the prothrombin time (line) and factor X level (bars).

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Animals in medical research: controversy in Europe and the United States

"**Sometimes distasteful, but** essentially unavoidable" summarizes the general attitude to animal experimentation of many experimental pharmacologists, physiologists, surgeons, anatomists, and psychologists. Recently, however, the traditional British gut reaction against cruelty to animals has led to an outbreak of press exposés on questionable laboratory practices.

The biomedical research organizations have usually kept their official response to an absolute minimum, and any information from them has been vague, placatory, and treated with some suspicion. The often-justifiable fear by researchers that experimental procedures would be reported out of context and their motives misunderstood by an uninformed public previously prompted them to avoid discussion on the part played by animal experimentation in their work. However, in recent years, there has been critical publicity focused on the secretive practices of many British professions, including those involved in animal experimentation.

A question that is now frequently being asked is whether the amelioration of one evil (disease) is sufficient excuse for the perpetration of another (vivisection). This question is not easy to answer, but animal welfare groups claim that scientists rarely acknowledge the issue, focusing instead on their individual projects.

SYMPTOMS OF DISQUIET

On July 23, 1983, a group of animal rights activists marched to the Wellcome Research Laboratories south of London and handed in a petition that asked Wellcome to spend some of its profits on seeking alternatives to animal experimentation.

This was just one example of many such demonstrations. In March of this year, members of a group called the Animal Liberation Front caused £12,000* worth of damage to the home of a man whom they claimed ran a company that exported dogs to Nigeria. In April, about 80 protesters forced doors open at the Imperial Chemical Industries research laboratories in Cheshire and filmed some of the animals there. In addition, several universities and medical schools have been raided by protesters demonstrating against experiments on animals.

Prior to the march on the Wellcome laboratories, Dr John Vane, director of research and development, stated that it was important to realize that the discovery and development of most of the medicines in use today would not have been possible without experiments on animals. In the same way, future breakthroughs in the treatment of disease would also depend upon animal experimentation.

A spokesman for the company said later that Wellcome was already contributing towards seeking alternatives to animal experimentation. The Fund for the Replacement of Animals in Medical Experiments (FRAME) has, in fact, received financial support from about 10 British pharmaceutical companies, amounting to a total of approximately £350,000. However, some critics consider this amount to be much too little, particularly when compared with the amount spent by the pharmaceutical industry on promotion and advertising.

A meeting of scientists from some of the major British pharmaceutical companies, which was held by FRAME in November 1983, agreed that the LD_{50} test—used to define the dose of a drug that would kill 50% of a test group of animals of a particular species—should be dropped as a routine safety assessment, because comparatively large groups of animals are necessary for the tests to be statistically valid. As a consequence of the increasing regulation of drug development, certain tests such as the LD_{50} are a mandatory part of every application to license a new medicine in the United Kingdom.

In March of this year, the Association of the British Pharmaceutical Industry agreed that there was no general need for the measurement of acute toxicity by determination of the LD_{50} value, except in special circumstances. The LD_{50} test appeared to be of limited importance in the development of medicines, and other methods for assessing acute toxicity were being adopted by the British pharmaceutical industry. Toxicologists suggest that limited acute toxicity studies should satisfy scientific and practical needs, without the LD_{50}'s requirement of large numbers of animals. Regulatory authorities are now moving away from their former reliance on the LD_{50} test.

Another area in which the overuse of animals has appeared questionable is that of psychological testing. Pharmacologists suspect that numerous animals have died in psychological experiments that cannot be justified scientifically. Dr Richard Ryder, a senior clinical psychologist at Warneford Hospital, Oxford, has outlined many psychological experiments that cause severe pain and distress in animals: these include experimental brain surgery, starvation, total isolation, the separation of infant monkeys from their mothers, and the deliberate creation of neurosis or helplessness through inescapable punishment or isolation. For example, the use of electric shock can cause severe physical pain in laboratory animals, and in 1982 there were over 36,000 experiments licensed in the UK that involved the use of electric shock and other aversive stimuli.

Dr Ryder claims that virtually nothing has been added to the understanding and treatment of mental illness by the inflicting of terror or other distress on laboratory animals. He maintains that absurdly inflated claims are made by experimental psychologists who work with animals, few of whom have contact with psychiatric patients. Furthermore, either animals are totally different from humans, in which case little can be gained from animal studies, or they are very similar in their emotions and cognition, and therefore they should be accorded a similar degree of respect.

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* 1£ = $1.24

EXTENT OF THE PROBLEM

Although the number of experimental procedures performed on living animals in Great Britain is declining, opponents claim that it is still too high. Home Office statistics show that the number of experiments in 1980 was 4.579 million, compared with 4.720 million in 1979 and a peak figure of 5.607 million in 1971. Experiments related to medical, dental, and veterinary products accounted for the bulk of the total and have shown only a slight decline, from 2.681 million to 2.680 million. Rodents, principally mice, were involved in 88% of the experiments in this category.

At the Ministry of Defence's Porton Down research establishment, 9,000 to 10,000 animal experiments were carried out on live animals in 1983, some without the use of anesthetics. Much indignation was aroused when it was learned that approximately 50 animals were deliberately wounded by being shot in ammunition tests to aid research into the treatment of wounds. Animals were also subjected to various chemical and biological agents when anesthetized. The animals used by the Ministry of Defence were mainly rats, mice, and guinea pigs, but pigs, rabbits, and monkeys were also used.

The government's position was that some of the experiments conducted at Porton Down required the use of animals to assist in improving methods used in the treatment of wounds. This assertion was supported by the claim that a drug tested on shot animals had had a dramatic impact during the Falklands conflict.

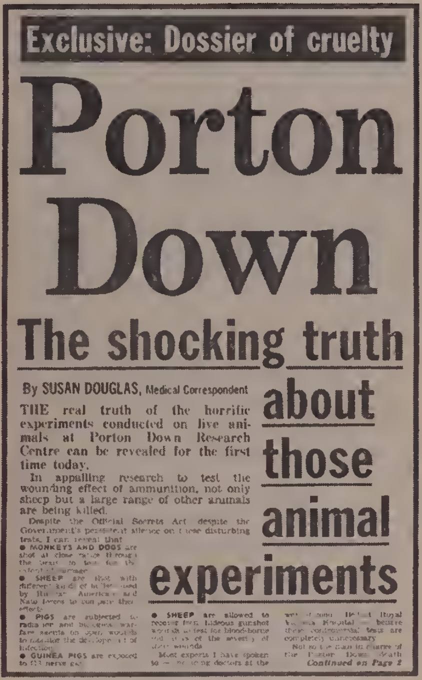
Commander Rick Jolly, who ran a field hospital at Ajax Bay, stated that metronidazole had been given with great success to soldiers who had been shot in the stomach or suffered shrapnel wounds. However, other doctors who specialize in war wounds—including some at the Royal Victoria Hospital in Belfast—disclaimed the usefulness of experiments like those carried out at Porton Down.

There was, therefore, a suspicion that animals were being shot so that more efficient weapons could be developed, rather than to save human lives. Another problem was that even the Cruelty to Animals Act did not necessarily apply to government departments.

ANIMAL RIGHTS

Although there is considerable controversy among contemporary philosophers on the notion of rights, of either human beings or animals, there is also a considerable body of evidence to suggest that a society's cruelty towards animals and violence towards humans have common causes. Animal welfare groups suspect that some scientists have been lax or careless in their treatment of animals, and that the implementation of better and less painful procedures would benefit the animals as well as the accuracy of research results.

These beliefs have prompted a call for more information and openness in the field of laboratory animal research procedures. It is maintained that researchers should accept the need to justify why a procedure had to be used at all, why the suffering inflicted could not be reduced, and why the number of animals involved could not be decreased. Animal rights groups argue that all experimental manipulation of animals is cruel and unnecessary unless it directly benefits the individual animals involved. From their point of view, the use of animals in research is a manifestation of "speciesism."



Exclusive: Dossier of cruelty

Porton Down

The shocking truth about those animal experiments

By SUSAN DOUGLAS, Medical Correspondent

THE real truth of the horrific experiments conducted on live animals at Porton Down Research Centre can be revealed for the first time today.

In appalling research to test the wounding effect of ammunition, not only sheep but a large range of other animals are being killed.

Continued on Page 2

The Mail, February 19, 1984. Front-page coverage of vivisection.

EUROPEAN REMEDIES

In Strasbourg, the Council of Europe has prepared a draft convention proposing a detailed system of control over the use of animals in laboratories. In Geneva, the Council for International Organizations of Medical Sciences has prepared a draft list of ethical principles to be applied to experiments involving animals. In Britain, at the end of last year, the prestigious Royal Society began drafting guidelines to be followed in animal experiments, to supplement the expected governmental legislation. The Royal Society's president, Sir Andrew Huxley, explained that the guidelines would attempt to cover details that could not be precisely defined by legislation. These guidelines would be issued jointly by the Royal Society and the Universities Federation for Animal Welfare.

It was accepted by the Royal Society that some restrictions on scientific inquiry were justified; however, it was maintained that the position upheld by the British Veterinary Association and FRAME—that any procedure involving more than "trivial" degrees of pain should generally be forbidden—was unduly restrictive.

It was suggested that "mild" or even "substantial" pain were permissible in "scientifically promising" experiments, but severe and short-lived pain should be permitted only very rarely, and enduring pain not at all.

At a more basic level, school examination boards have begun moves to reduce drastically the number of dissections carried out by students studying biology and zoology. This step may help reduce the acceptance level of vivisection by future researchers. Nevertheless, the examination boards still believe that dissection is a legitimate method of scientific inquiry and an effective means of teaching children about internal bodily structures.

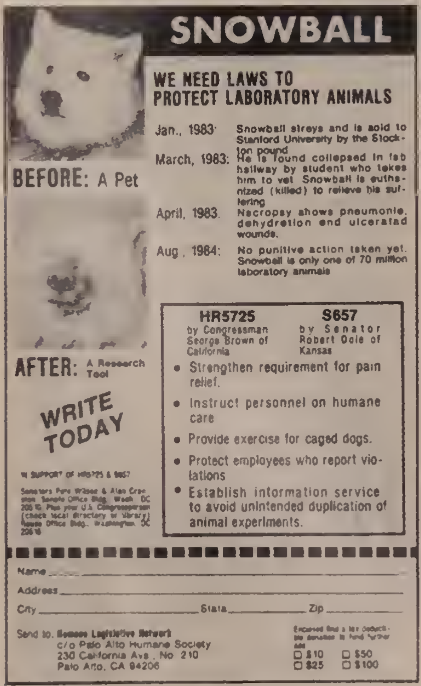
At the same time, British universities made it clear to the Home Office that they would object to paying for licenses for animal experiments, as anticipated in the impending government proposals. The Committee of Vice Chancellors and Principals wrote that "there would be a strong moral objection" to payment for personal or project licenses, because the work carried out at universities was intended to be of benefit to the whole community. The committee proposed the avoidance of emotive words in legislation, public statements, and the drafting of statistics. As an example, references to experiments that took place "without anesthetics" were cited: many of these were nutritional experiments and caused little or no discomfort to the animals concerned.

New Legislation Proposed

A joint working party of the British Veterinary Association, the Committee for the Reform of Animal Experimentation, and FRAME sent proposals for new legislation to the Home Secretary in April. This group claimed that their proposals represented an effective compromise between the welfare needs of the animals, the legitimate demands of the public for accountability, and the equally legitimate requirements of medicine, science, and commerce.

The report recommended that mice, rats, guinea pigs, rabbits, dogs, cats, and hamsters used in experiments should be obtained only from registered breeding establishments; this requirement would also apply to other species whenever possible. Lifetime records would be kept for each cat, dog, ungulate, and primate, showing the origin, lifetime movement, usage in procedures, and disposal of all animals.

One of the problems considered was that of defining pain, suffering, or distress. The working party suggested that the criterion for suffering should be the response of the animal to the stimulus, rather than the nature of the stimulus itself. The stress imposed in restraining and immobilizing an animal could be severe, whereas a brief painful stimulus, such as the insertion of a needle through the skin, was probably inconsequential.


BEFORE: A Pet
AFTER: A Research Tool
WRITE TODAY

SNOWBALL

WE NEED LAWS TO PROTECT LABORATORY ANIMALS

Jan., 1983:	Snowball strays and is sold to Stanford University by the Stockton pound
March, 1983:	He is found collapsed in lab hallway by student who takes him to vet. Snowball is euthanized (killed) to relieve his suffering
April, 1983.	Necropsy shows pneumonia, dehydration and ulcerated wounds.
Aug., 1984:	No punitive action taken yet. Snowball is only one of 70 million laboratory animals

HR5725 by Congressman George Brown of California

S657 by Senator Robert Dole of Kansas

- Strengthen requirement for pain relief.
- Instruct personnel on humane care
- Provide exercise for caged dogs.
- Protect employees who report violations
- Establish information service to avoid unintended duplication of animal experiments.

IN SUPPORT OF HR5725 & S657

Senators Pete Wilson & Alan Cranston, Senate Office Bldg., Wash. DC 20510. Plus your U.S. Congressperson (check local directory or library) House Office Bldg., Washington, DC 20515

Name ______

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Send to: Humane Legislative Network
c/o Palo Alto Humane Society
230 California Ave., No. 210
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Enclosed find a tax deductible donation to fund further ads
☐ $10 ☐ $50
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Newspaper advertisement appeal for money to lobby for laws defining animal experimentation.

The new legislation to control scientific experiments with living animals was proposed in a British government paper published in May. The current UK legislation was drawn up in 1876, and the new proposals would impose controls on a greater range of procedures involving animals in laboratories. Such legislation would require the registration of suppliers of animals for use in laboratories and would cover all aspects of the accommodation and care of animals in laboratories. The new system of licensing would aim to keep suffering to a minimum and ensure that alternative methods not involving animals were used whenever practicable.

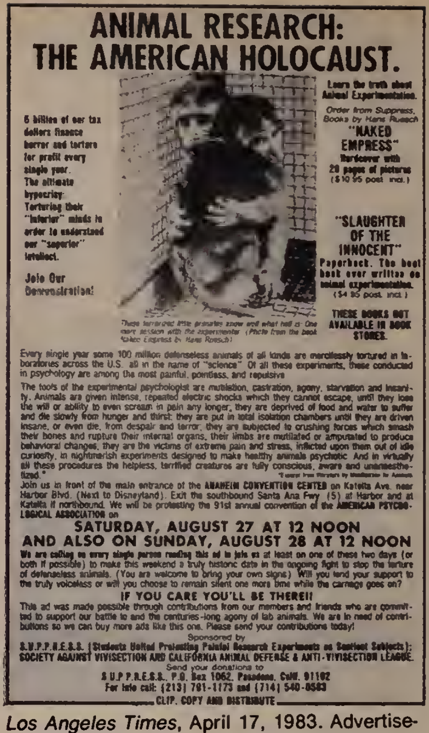
In Switzerland, a group working toward a complete ban on animal experiments has collected enough signatures to ensure that, under the federal constitution, a national referendum will be held on this question. Ciba-Geigy, the Swiss-based pharmaceutical company, has pointed out that such a ban would seriously jeopardize modern pharmaceutical research in Switzerland.

A sample poll in 1983 indicated that a majority of potential voters supported the referendum; however, as the vote will probably not take place until 1985, representatives of the influential Swiss pharmaceutical industry still have time to present their views. In the face of the possibility of a total ban, the pharmaceutical industry may regret not having taken earlier steps to improve and explain the necessity for the experimental procedures it uses.

Reactions from the United States

In the United States, controversy over animal experimentation has existed for over 100 years. An article published in the *New York State Journal of Medicine* in 1908 (8:606) referred to published denunciations of vivisection that were circulating in New York in the autumn of 1866. This had been followed by increasing demands for partial or total abolition of animal experimentation—countered in their turn by articles defending vivisection as synonymous with scientific advancement.

As newer organizations have grown more vocal, many have also grown more militant: in addition to polite discussions, some researchers have found themselves confronted with protests and bomb threats. Currently, animals have a large number of defenders in the United States: there are an estimated 400 animal rights groups with two million paid members and a great deal of political influence.



ANIMAL RESEARCH: THE AMERICAN HOLOCAUST.

6 billion of our tax dollars finance horror and torture for profit every single year.
The ultimate hypocrisy: Torturing their "inferior" minds in order to understand our "superior" intellect.

Join Our Demonstration!

These terrorized little primates know well what hell is: One more session with the experimenter. (Photo from the book Naked Empress by Hans Ruesch)

Learn the truth about Animal Experimentation.
Order from Suppress. Books by Hans Ruesch
"NAKED EMPRESS" Hardcover with 20 pages of pictures ($10.95 post. incl.)
"SLAUGHTER OF THE INNOCENT" Paperback. The best book ever written on animal experimentation. ($4.95 post. incl.)
THESE BOOKS NOT AVAILABLE IN BOOK STORES.

Every single year some 100 million defenseless animals of all kinds are mercilessly tortured in laboratories across the U.S. all in the name of "science". Of all these experiments, those conducted in psychology are among the most painful, pointless, and repulsive.

The tools of the experimental psychologist are mutilation, castration, agony, starvation and insanity. Animals are given intense, repeated electric shocks which they cannot escape, until they lose the will or ability to even scream in pain any longer; they are deprived of food and water to suffer and die slowly from hunger and thirst; they are put in total isolation chambers until they are driven insane, or even die, from despair and terror; they are subjected to crushing forces which smash their bones and rupture their internal organs; their limbs are mutilated or amputated to produce behavioral changes; they are the victims of extreme pain and stress, inflicted upon them out of idle curiosity, in nightmarish experiments designed to make healthy animals psychotic. And in virtually all these procedures the helpless, terrified creatures are fully conscious, aware and unanesthetized.*

*Excerpt from [illegible]

Join us in front of the main entrance of the **ANAHEIM CONVENTION CENTER** on Katella Ave. near Harbor Blvd. (Next to Disneyland). Exit the southbound Santa Ana Fwy. (5) at Harbor and at Katella if northbound. We will be protesting the 91st annual convention of the **AMERICAN PSYCHOLOGICAL ASSOCIATION** on

**SATURDAY, AUGUST 27 AT 12 NOON
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We are calling on every single person reading this ad to join us at least on one of these two days (or both if possible) to make this weekend a truly historic date in the ongoing fight to stop the torture of defenseless animals. (You are welcome to bring your own signs.) Will you lend your support to the truly voiceless or will you choose to remain silent one more time while the carnage goes on?

IF YOU CARE YOU'LL BE THERE!!

This ad was made possible through contributions from our members and friends who are committed to support our battle to end the centuries-long agony of lab animals. We are in need of contributions so we can buy more ads like this one. Please send your contributions today!

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Los Angeles Times, April 17, 1983. Advertisement for anti-vivisectionist protest at American Psychological Association meeting.

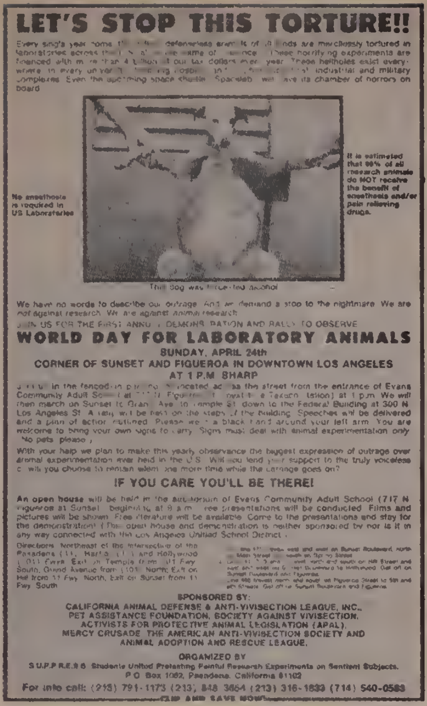
Older groups devoted to animal welfare have tended to work for legislative goals, and their efforts have had some effect. An increasing number of bills before Congress and state legislatures relate to laboratory animals—a reflection of rapidly increasing public concern, and proposed government policy changes relating to federal agencies would require institutions to provide more specific information on animal research programs. The care and use of all animals would be reviewed and approved by specially appointed committees. These committees would include lay members and would consider individual grant proposals entailing the use of research animals. As a last resort, National Institutes of Health funding could be withheld if the guidelines were violated.

In addition to questioning the basic ethics of animal experimentation, protest groups are asserting that much biomedical research is useless, or at least repetitive and poorly directed. This was the argument used in 1981 when Edward Taub, a behavioral researcher, was taken to court in Maryland on charges of cruelty to animals. Participants in a recent symposium sponsored by the National Coalition for Science and Technology have declared that researchers are now turning away from large-scale, unnecessary use of laboratory animals, in response to public opposition.

The Pharmaceutical Manufacturers Association has recommended that fewer animals be used in drug safety evaluations—provided that regulatory requirements can be suitably amended. Academic institutions are increasingly experimenting with bacteria, yeasts, fruit flies, cell cultures, and even computers in the toxicologic testing of chemicals, although, at a philosophical level at least, some of these potential subjects may be claimed to have "rights." The increasing cost of buying and maintaining laboratory animals has also forced a substantial decrease in the number of animals used in research in recent years: the National Academy of Sciences reported a 40% drop between 1968 and 1978.

However, most major advances in medicine have been based on animal research. As Robert J. Siegel, MD wrote in the *Los Angeles Times* earlier this year, animal research has resulted in the prolongation of the lives of millions with insulin-dependent diabetes, significant cures and improvements in survival rates for a number of cancers, the development of surgical methods for the repair of congenital defects, coronary artery bypass surgery, vaccines to prevent serious epidemics such as polio, smallpox, influenza, pertussis, and diphtheria, as well as the development of drugs that may cure or prevent progression of a vast array of diseases and give relief to or hasten the recovery of many patients.

Product testing involves the use of more animals than basic biomedical research. Investigations on a new drug or cosmetic require tests on a significant number of animals at a variety of dosage levels. Although the testing of medical products using animals causes some disquiet, in Britain much more indignation has been generated when the tests have been on less essential products such as cosmetics. Thus, although a test may be justifiable because of obvious product-quality or research requirements, a more intense public evaluation of overall priorities is beginning to emerge. Some United States institutions are setting up research evaluation boards to decide whether the results of proposed experiments are likely to be of enough significance to justify the animals' pain.



LET'S STOP THIS TORTURE!!

Every single year some [illegible] defenseless animals of all kinds are mercilessly tortured in laboratories across [illegible] in the name of science. These horrifying experiments are financed with more than 4 billion of our tax dollars every year. These hellholes exist everywhere in every university, [illegible] industrial and military complexes. Even the upcoming space shuttle "Spacelab" will have its chamber of horrors on board.

No anesthesia is required in US Laboratories

It is estimated that 90% of all research animals do NOT receive the benefit of anesthesia and/or pain relieving drugs.

This dog was force-fed alcohol

We have no words to describe our outrage. And we demand a stop to the nightmare. We are not against research. We are against animal research.

JOIN US FOR THE FIRST ANNUAL DEMONSTRATION AND RALLY TO OBSERVE

WORLD DAY FOR LABORATORY ANIMALS

SUNDAY, APRIL 24th

CORNER OF SUNSET AND FIGUEROA IN DOWNTOWN LOS ANGELES

AT 1 P.M. SHARP

[illegible] in the fenced-in parking lot located across the street from the entrance of Evans Community Adult School at [illegible] Figueroa [illegible] Texaco station) at 1 p.m. We will then march on Sunset to Grand Ave. to Temple St. down to the Federal Building at 300 N. Los Angeles St. A rally will be held on the steps of the building. Speeches will be delivered and a plan of action outlined. Please wear a black band around your left arm. You are welcome to bring your own signs to carry. Signs must deal with animal experimentation only. (No pets, please.)

With your help we plan to make this yearly observance the biggest expression of outrage over animal experimentation ever held in the U.S. Will you lend your support to the truly voiceless or will you choose to remain silent one more time while the carnage goes on?

IF YOU CARE YOU'LL BE THERE!

An open house will be held in the auditorium of Evans Community Adult School (717 N. Figueroa at Sunset) beginning at 9 a.m. Free presentations will be conducted. Films and pictures will be shown. Free literature will be available. Come to the presentations and stay for the demonstration! (The open house and demonstration is neither sponsored by nor is it in any way connected with the Los Angeles Unified School District.)

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CLIP AND SAVE NOW

Los Angeles Times, August 21, 1983.

Scientists tend to prefer non-animal methods when they are appropriate, because animal studies are costly and time-consuming. In the United States there is a comparatively cheap supply of there is a comparatively cheap supply of animals from pounds, whereas a similar source of laboratory animals is not available in countries such as Britain. The current United States campaign to ban research on animals that have been scheduled for destruction at the local pound is causing much concern to researchers and their employers. If these pound animals became unavailable, costs would increase, and projects could be delayed.

The numerous regulatory requirements for animal tests, coupled with high litigation risks if a product can be claimed to have been insufficiently tested, may have caused the utilization of comparatively more test animals than in Europe. Will the public be prepared to accept higher product costs or less stringent safety tests, or both if laboratory animals become even more expensive? And can anyone give an unbiased assessment of how these factors will affect the price or availability of a particular medical product? Ironically, the medical advances gained by animal experimentation may themselves be indirectly responsible for the elevation of animal welfare considerations to the level of concern for human health.

PROGNOSIS UNCERTAIN

So far the UK has not seen a complete polarization of attitudes on animal experimentation. As in the US, an area of common interest between most groups concerned with animal experimentation is the initial concentration on more humane practices; it is hoped that improvements in the conditions in which animals are housed, and the consequent reduction in stress to the animals, will also lead to more accurate and reliable experimental findings and a reduction in the variability and numbers of experiments undertaken.

The overlap between the membership of animal welfare organizations and alternative health promotion groups may indicate that a long-term aim of reducing animal experimentation in medical research could evolve from an increasing interest in preventing disease by reducing stress, exercising more, not smoking or using other drugs, and improving diet—including a reduction in the consumption of animal products.

R J Woodhouse

Mr Woodhouse is a medical and science writer in Wiltshire, England.

THE ADMINISTRATION OF A PUBLIC HEALTH AGENCY: A CASE STUDY OF THE NEW YORK CITY DEPARTMENT OF HEALTH.

By Pascal James Imperato, MD. 226 pp. New York, Human Sciences Press, 1983. $26.95.

The New York City Department of Health is the largest local public health department in the country and has long been a model for other health departments in the United States and abroad. Dr Imperato, an internationally known public health specialist and a former Commissioner of Health of New York City, has written a critical analysis of this department and its functions for the period 1965–1981. He has brought to this effort broad public health experience in Africa, South America and the United States, meticulous scholarship, first hand knowledge of the department and excellent writing abilities, all of which make this book a definitive portrait of public health in the city for the period under study.

Against the background of New York City's social and economic problems and its underlying political fabric, the author sharply focuses on the major issues, problems and administrative changes encountered by the department over a 17-year period. In the first chapter, he provides an overview of New York City, covering demography, employment trends, housing, social problems, crime and the major political events that spanned the administrations of four mayors—Wagner, Lindsay, Beame, and Koch. This is followed by a chapter on the early history of the department, covering the period of 1657–1933 and one on its more recent history, 1934–1970. The fourth chapter deals with the Health Services Administration, established in 1966 by Mayor John Lindsay. The author relates that this super-agency eclipsed the health department, introduced some beneficial project management techniques into it, but at the same time politicized it in the interests of Lindsay's efforts to secure the Democratic presidential nomination.

The fifth chapter describes how the department was re-professionalized under Mayor Abraham Beame and his first health commissioner, Lowell E. Bellin, MD. New York City's fiscal crisis is dealt with in great detail, the author providing extensive information on how it affected the health department. This chapter ends with a discussion of how the department fared during Mayor Edward Koch's first term. The author states that the department rapidly deteriorated during this period, losing many of its superior quality professionals and numerous functions. The author argues that this came about for several reasons. The city administration assigned a low priority to public health, effective public health constituencies were absent, and the health commissioner of the day allowed city hall to dictate public health policy. He goes on to say that the Koch administration was eventually embarrassed by the department's condition and that during his second term the mayor made some efforts to turn the situation around.

Chapter six explains the structure and functions of the department and chapter seven describes the board of health. The next chapter, entitled The Chief Executive, is a fascinating account of how commissioners of health are chosen, their relations with mayors and deputy mayors, and provides interesting historical accounts of the difficulties encountered by various commissioners who upheld professional standards and, in the process, antagonized the mayors who had appointed them.

The next three chapters, Establishing Priorities, The Budget, and The Decision Making Process are must reading for any physician with administrative responsibilities. They contain a wealth of information on how organizations function.

In chapter twelve the author carefully analyzes the relationship between the state and city health departments and extensively describes the Health Czar proposal put forth by the state in 1977. The final chapter, entitled Dealing With the Press and Media, provides many useful insights into how the press and media function and relate to public health officials. This is followed by nineteen pages of reference notes and an extensive index. The book is appropriately dedicated to the late King Humbert II of Italy who was actively interested in international public health and welfare programs.

The Administration of a Public Health Agency is not only a milestone publication in public health, but also the personal story of a physician who faced the many crises of his health commissionership with the same professionalism that had earlier marked his career in East and West Africa. The author is a keen observer and scrupulously objective, drawing his information from diverse sources, including published materials, personal interviews and his own substantial experience. This engaging book is must reading for present and future health care administrators, public health physicians and students of government. It is highly recommended to all those who have an interest in New York City, public health, public policy and administration.

HANA ROSTAIN, MD
New York University Medical Center
New York City 10016

MEDICAL EXAMINATION REVIEW: PHYSICAL DIAGNOSIS

Second edition. By John H. Holbrook, MD. 225 pp. New York, Medical Examination Publishing Co, Inc, 1983. $12.75

Holbrook has revised his book *Medical Examination Review: Physical Diagnosis*. The book provides an engaging and painless means to refine one's knowledge of bedside diagnosis, and to deepen it. Six hundred multiple-choice and multipart true-false questions precede brief, annotated descriptive answers. The chapters are organized by both regional (abdominal, for example) and systemic (lymphatic, for example) examination. Most questions concern physical examination, some encompass symptoms and other aspects of the history, and a few, such as that on malignant hyperthermia, have only a forced connection to either.

The preface states a modest aim of the book: self-assessment in bedside diagnosis. Most readers will use it not only to survey their knowledge, but also to increase it. Questions range from the everyday, "what physical finding most suggests right ventricular enlargment?" to intriguing rarities, "what ophthalmoscopic feature of choroidal melanoma best distinguishes it from benign nevus?" One learns that assumptions about many commonplace entities prove groundless. After six years of teaching physical diagnosis, this reviewer missed 24% of the questions overall, with a lowest score of 40% wrong in the chapter on musculoskeletal diseases. Humbled and better-informed, one becomes eager to delve into the references.

The breadth of subject matter is appealing. This is a book for all doctors. In offering a real challenge, these questions contrast with other current bedside texts, which address the student rather than the graduate or attending physician, and so this small book is a worthwhile addition to the medical literature.

The 102 references to which the annotations are keyed include standard texts in physical diagnosis, internal medicine, medical and surgical subspecialties, and 34 journal articles. Although current through 1982, the references omit material vital even to a summary bibliography.

Inevitably, one disagrees with certain emphases. For instance, the assertion that stony hepatomegaly in a 52-year-old most likely represents carcinomatosis and not chronic myelogenous leukemia, while statistically true, undercuts the lesson that heart failure, cirrhosis, and hepatitis do not produce hard, enlarged livers. Tabes dorsalis is inappropriately equated with neurosyphilis and with the Argyll-Robertson pupil. A misprint magnifies a glomus tumor 10 times.

One learns lessons that have immediate application; for example, exacerbation of otalgia by moving the pinna characterizes otitis externa and not media. Furthermore, with the answer to question 116, I confidently diagnosed the yellow pinheads on a student's buccal mucosa, which had so alarmed his physical diagnosis partner. Perhaps 10% of the questions have predominantly academic interest, as does the news that bluish ears and black cerumen suggest ochronosis. Some questions suit a well-rounded experience: large orange tonsils predict high-density lipoprotein (HDL) deficiency.

Overall, attention to this subject can only improve the quality of one's practice. The intellectual gratification of making a subtle diagnosis with eyes, ears, and hands renders continual restudy of bedside diagnosis worthwhile. This book provides an agreeable means of continuing medical education.

HENRY SCHNEIDERMAN, MD
University of Connecticut
Health Center
Farmington, CT 06032

THE ATHLETIC EYE

By Arthur Seiderman, OD and Steven Schneider. 207 pp, illustrated. New York, William Morrow and Company, Inc, 1983. $14.95 (hardcover).

This book is devoted to the diagnosis and management of visual problems in the competitive athlete. It is directed primarily at the lay sector, though it may be of use to physicians practicing sports medicine. The 13 chapters are devoted to the various static and dynamic components of vision. Emphasis is placed on dynamic skills (tracking, hand-eye coordination, reaction time). Each chapter consists of a brief review of the subject, with a variety of testimonials from well-known athletes. There is a "how-to" section in which specific drills and exercises are outlined. The text concludes with special sections on vision and the child athlete, sports psychology, and a 30-day home sports vision training program. The sports psychology chapter deals with the relationship of visual skills to the psychologic profile of the athlete.

It is not possible to compare this book to other works in the field, as there are none. However, there has been a resurgent interest in the visual aspects of competitive athletics, particularly when they translate into victory. Though there has been some research done by NASA, the military services, and reserach scientists, there have been no carefully controlled research studies evaluating the methodologies suggested in *The Athletic Eye*. As a result, the book suffers from an anecdotal style unsupported by experimental work. The bibliographic references cite the work of laymen and professionals. The former are general in nature, while the latter are from the optometric literature and do not include controlled trials to support the authors' contentions.

In summary, *The Athletic Eye* represents a novel approach to improving an athlete's competitive edge through vision skills enhancement. Although the suggested exercises and drills may prove to have an impact on athletic performance, the book does not stand on a firm scientific base, and therefore, is not recommended for the sports physician.

RICHARD BIRRER, MD
State University of New York
Downstate Medical
Center
New York City 11203

CARDIOVASCULAR REHABILITATION: A COMPREHENSIVE APPROACH

Edited by Lysle H. Peterson, MD. 363 pp, illustrated. New York, Macmillan Publishing Co, 1983. $32.00 (hardcover)

The theme of this well written book is the many ramifications of cardiovascular rehabilitation. The book details the important facets of a properly orchestrated program for secondary prevention of cardiovascular disease, most specifically coronary artery disease, and discusses methods of treatment that enable the patient to resume an active and productive lifestyle. It is hoped that this would include returning to his or her former employment status, with necessary modifications to meet the patient's physical and emotional needs.

Peterson's initial point of concern is the development of a center for rehabilitation as a freestanding facility rather than a hospital-oriented program. It is this reviewer's opinion that the principles of development of a cardiac rehabilitation program will not differ greatly whether the facility is freestanding or hospital based.

The author bases his observations of approximately five years of experience in operating a freestanding cardiac rehabilitation unit in a large metropolitan center, recognized as a cardiovascular center of excellence. His writing style is impressive; he covers the essentials in a comprehensive and detailed, yet easily read and understood manner. In addition, he has brought in other specialists so as to provide specific and informative data regarding not only cardiac rehabilitation but also the general practice of cardiovascular medicine and its many subspecialties.

The material is divided into sections which address topics such as exercise tolerance testing, including data on hemodynamic principles and their significance in exercise testing and therapy. There is also an excellent chapter on ergometry—a subject this reviewer found not only interesting but quite informative. Other segments which deal with psychological aspects and dietary assessment and management are all very pertinent. In addition, the author discusses the diagnosis and treatment of coronary artery disease as well as methods of surgical intervention. Another interesting feature, not often seen in such books, is a discussion of the role of third party insurance carriers and other "interested parties" who deal with the costs of health care.

This book is a useful addition to the medical literature on cardiovascular disease and is an excellent reference book for practitioners in the field of cardiology as well as persons involved in the rehabilitation of patients with cardiac problems. Many useful tables and illustrations provide information that can be incorporated into both old and new programs in cardiovascular rehabilitation. The material presented compares very favorably, both in content and usefulness, with other books written on this subject and is presented in a well-organized and clear manner.

DAVID LONG, MD
The Heart Lung Center
St.Luke's Hospital
Phoenix, AZ 85006

REHABILITATION IN THE AGING

Edited by T. Franklin Williams, MD. 389 pp, illustrated. New York, Raven Press, 1983. $39.50 (hardcover).

"Rehabilitation and the aged," however one defines the latter, can be paired in much the same way as "disability and aging." This book is one of the few to be published in the last 10 years that addresses this topic.

The editor has assembled an outstanding group of experts who are well qualified to speak on the major medical, surgical, psychiatric and social problems that confront the aged. The authors have contributed well written and concise chapters. The editor has not attempted to offer a definitive textbook, but rather a volume dealing with the major areas of disability in the aged. References are provided for more extensive information. Unfortunately, it appears that constraints were applied to the authors, or the book would have included more than two pages describing osteoarthritis and 10 pages on pulmonary diseases.

This volume will be of interest to psychiatrists, family practitioners, and internists. The chapters on psychiatry, sexuality, social problems, aspects of pharmacokinetics and the physiologic basis of rehabilitation therapy are informative and provide good background for other major medical problems. This volume will also be of interest to therapists, nurses and other personnel involved in caring for the aged.

The authors identify the more significant disorders such as heart disease, stroke, arthritis, and urologic, vascular, foot, dental, and communication problems. Specific rehabilitation supports to reduce the limitations of the disabled are also well described. Descriptions of safety, home care, recreation, architectural design, institutional services, pastoral care, and the economics of being old are only touched upon. I would have liked to see more information presented on these issues.

The sad fact is that there is no definitive volume covering the care of the aged such as exists for pediatrics or medicine. Considering that there are 48 million Americans over 55 years of age, the need for such a text is obvious. Despite its brevity, I think this is a fine volume and well worth reading.

SAMUEL S. SVERDLIK, MD
St. Vincent's Hospital
and Medical Center
New York City 10011

THE BREAST

Edited by Robert W. McDivitt, MD, Harold A. Oberman, MD, Luciano Ozzello, MD and Nathan Kaufman, MD. 209 pp, illustrated. Baltimore, Waverly Press, Inc, 1984. $45.00 (hardcover)

This monograph is a collection of nine single-authored chapters based upon presentations at the 72nd annual meeting of the United States-Canadian Division, International Academy of Pathology, held in March 1983. Unlike the broad scope of previous monographs, *The Breast*, as stated in the preface, "presents a summary of current information pertaining to a specific topic that otherwise would be difficult to obtain without an extensive search of the literature."

A very favorable acceptance of this monograph by pathologists engaged in evaluating surgical specimens is virtually assured by the fact that customary "diagnosis and extent of disease" is no longer an adequate assessment. Care of patients with cancer is a collaborative function between patient, primary physician, surgeon, chemotherapist, radiotherapist and the pathologist, who may assess histologic factors. These variables include mitotic rate, histologic and nuclear anaplasia, tubule formation, vascular and lymphatic permeation and metastasis. They must be assessed accurately so as to permit predictions of mortality risks, recurrences, and responses to various therapies. This monograph covers all of these components.

The chapter "Benign breast lesions confused with carcinoma" is of immediate and direct interest to every surgical pathologist. Nine benign lesions in which the differential diagnosis of carcinoma arises more commonly are analyzed in a lucid and objective manner. One fifth of the monograph is devoted to a discussion of lobular carcinoma in situ and intraductal carcinoma. Considerable emphasis is placed on historical perspectives.

Other excellent chapters include "Ultrastructure of epithelial proliferations," "Breast cancer multicentricity," "Diagnostic imaging of the breast," and "Mammary needle biopsy."

Cytology and tissue core histology can provide diagnoses in given situations. However, information beyond a diagnosis is so important in good patient care that this procedure is not likely to gain wide acceptance unless economic factors become overriding.

Lastly, the role of steroid receptors as indicators of response to hormone therapy is discussed. There is promise that new studies of tumor cell kinetics (tritiated thymidine labeling of cells and flow cytometric analysis of cellular DNA content) will have a role in selection of patients for timely cytotoxic chemotherapy.

JOSEPH F. KUZMA, MD
Family Hospital
Milwaukee, WI 53208

OBITUARIES

In addition to these listings, the Journal *will publish obituaries written by physician readers. Inquiries should first be made to the Editor.*

Joy Kathleen Baisinger, MD, Hyde Park. Died July 20, 1984; age 33. She was a 1977 alumna of the University of Washington School of Medicine. Dr Baisinger was a Diplomate of the American Board of Internal Medicine, and was a member of the American Thoracic Society, the Dutchess County Medical Society and the Medical Society of the State of New York.

Tamara Ballard, MD, New York. Died July 3, 1984; age 71. Dr Ballard was a 1939 alumnus of the Università degli Studi di Bologna, Facoltà di Medicina e Chirurgia and was a member of the New York County Medical Society and the Medical Society of the State of New York.

William M. Bennett, MD, Tamarac, Florida. Died July 4, 1984; age 77. He was a 1935 graduate of the Licentiate of the Royal College of Physicians of Edinburgh. Dr Bennett was a Fellow of the American Academy of Family Physicians, and a member of the New York Cardiological Society, the Medical Society of the County of Kings and the Medical Society of the State of New York.

Marvin Bernstein, MD, Commack. Died July 26, 1984; age 47. Dr Bernstein was a 1962 alumnus of the Albert Einstein College of Medicine of Yeshiva University. He was a member of the Suffolk County Medical Society and the Medical Society of the State of New York.

Samuel Dearborn Bird, MD, Freeport. Died July 26, 1984; age 77. He was a 1933 graduate of New York University College of Medicine. Dr Bird was a Fellow of the American Academy of Family Physicians and a member of the Academy of Medicine, the Nassau County Medical Society and the Medical Society of the State of New York.

Claude B. Cave, MD, Brooklyn. Died July 2, 1984; age 74. Dr Cave was a 1938 graduate of the Loma Linda University School of Medicine. He was a member of the American Academy of Family Physicians, the Medical Society of the County of Kings and the Medical Society of the State of New York.

Jack Chalon, MD, Tarrytown. Died June 19, 1984; age 64. He was a 1962 alumnus of the University of London Faculty of Medicine, London. Dr Chalon was a Fellow of the American College of Chest Physicians and the American College of Angiology, and a Diplomate of the American Board of Anesthesiology. His memberships included the Academy of Medicine, the American Society of Anesthesiologists, Inc, the New York County Medical Society and the Medical Society of the State of New York.

Isaac Chomski, MD, New York. Died July 3, 1984; age 81. He was a 1941 graduate of the Université de Montpellier Faculté de Médicine, Montpellier. Dr Chomski was a member of the New York County Medical Society and the Medical Society of the State of New York.

Arthur J. Cramer, Jr, MD, Williamsville. Died July 21, 1984; age 76. Dr Cramer was a 1932 graduate of the University of Buffalo School of Medicine. He was a Diplomate of the American Board of Pediatrics, and a member of the Academy of Medicine, the American Academy of Pediatrics, the Medical Society of the County of Erie and the Medical Society of the State of New York.

William Henry Dwinelle, MD, Inverness, Florida. Died May 21, 1984; age 67. Dr Dwinelle was a 1942 alumnus of the State University of New York Upstate Medical Center. He was a member of the Medical Society of the County of Oswego and the Medical Society of the State of New York.

Ernest Ronald Esakof, MD, Forest Hills. Died June 28, 1984; age 57. He was a 1952 alumnus of the University of Witwatersrand Medical School, Johannesburg. Dr Esakof was a Fellow of the American College of Chest Physicians, and a member of the New York Cardiological Society, the American Thoracic Society, the New York County Medical Society and the Medical Society of the State of New York.

Gerald Flaum, MD, Newburgh. Died July 4, 1984; age 74. He was a 1933 alumnus of New York University College of Medicine. Dr Flaum was a Fellow of the American College of Physicians and a Diplomate of the American Board of Internal Medicine. His memberships included the Academy of Medicine, the New York State Society of Internal Medicine, the Endocrine Society, the American Society of Internal Medicine, the Medical Society of the County of Orange and the Medical Society of the State of New York.

Albin Gedarovich, MD, Bayside. Died August 9, 1984; age 61. He was a 1946 alumnus of Columbia University College of Physicians and Surgeons. Dr Gedarovich was a Diplomate of the American Board of Pediatrics and a member of the American Academy of Pediatrics, the Medical Society of the County of Queens and the Medical Society of the State of New York.

Herbert B. Gianfrancesco, MD, Roslyn. Died May 21, 1984; age 67. He was a 1944 graduate of Boston University School of Medicine. Dr Gianfrancesco was a Fellow of the American College of Surgeons, a Diplomate of the American Board of Surgery and a Diplomate of the American Board of Thoracic Surgery.

He was a member of the Nassau County Medical Society and the Medical Society of the State of New York.

Jerome J. Goldstein, MD, Long Beach. Died July 6, 1984; age 68. He was a 1940 graduate of New York Medical College, Flower and Fifth Avenue Hospitals. Dr Goldstein was a Fellow of the American College of Surgeons and a Diplomate of the American Board of Ophthalmology. He was a member of the New York Society for Clinical Ophthalmology, the American Academy of Ophthalmology, the Nassau County Medical Society and the Medical Society of the State of New York.

Leo Gottesman, MD, New York. Died August 4, 1984; age 90. He was a 1921 graduate of the Medizinische Fakultät der Universität, Vienna. Dr Gottesman was a member of the Medical Society of the County of Queens and the Medical Society of the State of New York.

David Gutman, MD, Eastchester. Died July 2, 1984; age 75. He was a 1933 alumnus of Universita Komenského Fakulta Lekárska, Bratislava. Dr Gutman was a Fellow of the American Academy of Family Physicians and a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Robert Carr Hall, MD, Alexandria Bay. Died July 14, 1984; age 91. Dr Hall was a 1920 alumnus of the University of Toronto Faculty of Medicine, Toronto. He was a member of the Medical Society of the County of Oneida and the Medical Society of the State of New York.

Kurt Holzer, MD, Poughkeepsie. Died June 15, 1984; age 82. Dr Holzer was a 1925 graduate of Friedrich-Wilhelms-Universität Medizinische Fakultät, Berlin, Prussia. He was a member of the American Geriatrics Society, the Dutchess County Medical Society and the Medical Society of the State of New York.

James S. Kaufman, MD, Jamaica. Died July 24, 1984; age 76. Dr Kaufman was a 1934 graduate of the University of Edinburgh Faculty of Medicine, Edinburgh. He was a member of the Medical Society of the County of Queens and the Medical Society of the State of New York.

Harry James Kerrigan, Jr, MD, Yonkers. Died July 12, 1984; age 62. He was a 1947 alumnus of New York Medical College, Flower and Fifth Avenue Hospitals. Dr Kerrigan was a Fellow of the American College of Anesthesiologists and a Diplomate of the American Board of Anesthesiology. He was a member of the New York State Society of Anesthesiologists, the American Society of Anesthesiologists, Inc, the Medical Society of the County of Westchester and the Medical Society of the State of New York.

Israel Kibel, MD, Bronxville. Died June 16, 1984; age 86. He was a 1923 alumnus of New York University College of Medicine. Dr Kibel was a Fellow of the American College of Obstetricians and Gynecologists, and a Qualified Fellow of the International College of Surgeons. He was a member of the Bronx County Medical Society and the Medical Society of the State of New York.

Elliott Konis, MD, New York. Died July 28, 1984; age 73. He was a 1939 graduate of Uniwersytet Stefana Batorego Wydzial Lekarski, Wilno. Dr Konis was a Fellow of the American Academy of Family Physicians, the New York County Medical Society and the Medical Society of the State of New York.

Michael Lake, MD, New York. Died May 24, 1984; age 87. Dr Lake was a 1922 graduate of Cornell University Medical College. He was a Fellow of the American College of Physicians and a Diplomate of the American Board of Internal Medicine. His memberships included the Academy of Medicine, the New York Gastroenterological Society, the American Public Health Association, the New York County Medical Society and the Medical Society of the State of New York.

Jacob Moses Leavitt, MD, Williamsville. Died September 5, 1983; age 84. He was a 1930 graduate of New York University College of Medicine. Dr Leavitt was a Fellow of the American College of Gastroenterology. His memberships included the New York Gastroenterological Society, the New York Academy of Gastroenterology, the New York County Medical Society and the Medical Society of the State of New York.

Herbert Lewy, MD, Rochester. Died May 25, 1984; age 85. Dr Lewy was a 1923 graduate of Friedrich-Wilhelms-Universität Medizinische Fakultät, Berlin, Prussia. He was a member of the Academy of Medicine, the Medical Society of the County of Monroe and the Medical Society of the State of New York.

George Lichtenfeld, MD, New York. Died July 12, 1984; age 84. He was a 1924 alumnus of Friedrich-Wilhelms-Universität Medizinische Fakultät, Berlin, Prussia. Dr Lichtenfeld was a member of the New York County Medical Society and the Medical Society of the State of New York.

Vincent S. Maggio, MD, Hampton Bays. Died August 3, 1984; age 81. Dr Maggio was a 1929 graduate of Harvard Medical School. He was a Fellow of the American College of Surgeons and a member of the American Geriatrics Society, the Medical Society of the County of Kings and the Medical Society of the State of New York.

Harold R. Merwarth, MD, Garden City. Died August 20, 1984; age 89. He was a 1921 alumnus of Harvard Medical School. Dr Merwarth was a Fellow of the American College of Physicians, and a member of the Academy of Medicine, the American Psychiatric Association, the Medical Society of the County of Kings and the Medical Society of the State of New York.

Charles R. Messeloff, MD, New York. Died August 7, 1984; age 81. He was a 1926 graduate of New York University College of Medicine. Dr Messeloff was a Fellow of the American College of Physicians and a Diplomate of the American Board of Internal Medicine. He was a member of the American Geriatrics Society, the Bronx County Medical Society and the Medical Society of the State of New York.

Felix Henry Metis, MD, Ridge. Died June 24, 1984; age 88. Dr Metis was a 1923 graduate of Schlesische-Friedrich-Wilhelms-Universität Medizinische Fakultät, Breslau, Prussia. He was a member of the Medical Society of the County of Queens and the Medical Society of the State of New York.

Angelo S. Naples, MD, Tonawanda. Died July 21, 1984; age 81. Dr Naples was a 1931 alumnus of the University of Buffalo School of Medicine. His memberships included the Academy of Medicine, the American Psychiatric Association, the American Geriatrics Society, the Medical Society of the County of Erie and the Medical Society of the State of New York.

Kamil Jaromir Neuman, MD, Delray Beach, Florida. Died July 5, 1984; age 87. Dr Neuman was a 1922 graduate of the Universita Karlova Fakulta Lekarska, Praha. He was a member of the American Academy of Family Physicians, the Medical Society of the County of Schenectady and the Medical Society of the State of New York.

Judson Adams Pillsbury, MD, Rochester. Died June 9, 1984; age 46. Dr Pillsbury was a 1965 alumnus of the University of Rochester School of Medicine and Dentistry. He was a member of the American Psychiatric Association, the Medical Society of the County of Monroe and the Medical Society of the State of New York.

Irving Rappaport, MD, Flushing. Died June 5, 1982; age 75. He was a 1934 graduate of Temple University School of Medicine. Dr Rappaport was a member of the Medical Society of the County of Queens and the Medical Society of the State of New York.

Charles Rieger, MD, Little Silver, New Jersey. Died July 18, 1984; age 95. He was a 1915 graduate of New York University College of Medicine. Dr Rieger was a member of the Richmond County Medical Society and the Medical Society of the State of New York.

Chris Geo Ronson, MD, Watertown. Died July 5, 1984; age 71. Dr Ronson was a 1940 alumnus of the State University of New York Upstate Medical Center. He was a Fellow of the American Academy of Family Physicians and a member of the Medical Society of the County of Jefferson and the Medical Society of the State of New York.

Isadore H. Sackadorf, MD, Miami Beach, Florida. Died July 27, 1984; age 88. Dr Sackadorf was a 1918 alumnus of New York University College of Medicine. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Murray Earle Sagat, MD, New York. Died April 24, 1984; age 76. He was a 1933 graduate of New York University College of Medicine. Dr Sagat was a member of the Bronx County Medical Society and the Medical Society of the State of New York.

Garrett W. Vink, MD, Carmel. Died July 6, 1984; age 77. Dr Vink was a 1932 graduate of Albany Medical College of Union University. He was a member of the Putnam County Medical Society and the Medical Society of the State of New York.

Charles Kalman Visoli, MD, Sarasota, Florida. Died June 4, 1984; age 76. He was a 1935 alumnus of Eotvos Lorand Tudomanyegyetem Orvostudomanyi Fakultas, Budapest. Dr Visoli was a member of the American Psychiatric Association, the Medical Society of the County of Erie and the Medical Society of the State of New York.

Stanley W. Widger, MD, Rochester. Died July 21, 1984; age 74. He was a 1937 alumnus of the University of Rochester School of Medicine and Dentistry. Dr Widger was a Fellow of the American College of Surgeons and a Diplomate of the American Board of Surgery. He was a member of the Medical Society of the County of Monroe and the Medical Society of the State of New York.

Frederick William Wood, MD, Vestal. Died August 12, 1984; age 65. He was a 1944 graduate of Harvard Medical School. Dr Wood was a Fellow of the American College of Surgeons and a Diplomate of the American Board of Surgery. He was a member of the Academy of Medicine, the Broome County Medical Society and the Medical Society of the State of New York.

Frederick Ziman, MD, New York. Died June 20, 1984; age 81. Dr Ziman was a 1928 graduate of New York Medical College, Flower and Fifth Avenue Hospitals. His memberships included the Academy of Medicine, the New York Society for Physical Medicine and Rehabilitation, the American Rheumatism Association, the American Geriatrics Society, the American Academy of Physical Medicine and Rehabilitation, the New York County Medical Society and the Medical Society of the State of New York.

Julius Stephen Zufa, MD, New York. Died April 24, 1984; age 83. Dr Zufa was a 1927 graduate of New York University College of Medicine. He was a member of the New York County Medical Society and the Medical Society of the State of New York.

Morton H. Zwerling, MD, New York. Died May 21, 1984; age 72. He was a 1936 graduate of the Universität Zurich Medizinische Fakultät, Zurich. Dr Zwerling was a member of the American Psychiatric Association, the American Psychoanalytic Association, the New York County Medical Society and the Medical Society of the State of New York.

Guidelines for authors

ORIGINALITY

The *New York State Journal of Medicine* welcomes research papers and original essays on the practice of medicine, medical education, public health, the history of medicine, medicolegal matters, legislation, ethics, the mass media and socioeconomic issues in health care.

Manuscripts should be prepared according to the "Uniform requirements for manuscripts submitted to biomedical journals" (*NY State J Med* 1983; 83:1089–1094). The requirements were established by the International Committee of Medical Journal Editors, of which the *Journal* is a participating member. These Guidelines are intended to highlight aspects of the *Journal*'s particular style of publication.

A manuscript will be considered for publication if it is original, has not been published previously in whole or in part in either a medical journal or a lay publication, and is not simultaneously under consideration elsewhere. A copy of any possibly duplicative material, such as a reference "in press," should be submitted along with the manuscript.

PREPARATION

An original typewritten or "word-processed" manuscript and two photocopies (to facilitate outside review) are required. If the manuscript is not accepted for publication, the original and one copy will be returned. All figures must be submitted in triplicate. The manuscript should be double-spaced throughout, including references, tables, legends, quotations, and acknowledgments. A separate title page should include the full title of the paper in upper and lower case type, the names of the authors exactly as they should appear in print (including their highest academic degree), an abbreviated title of no greater than 40 spaces for use as a running foot, and the names of all providers of funding for research on which the paper is based. Information on the amount and allocation of funding is optional.

A corresponding author should be designated in the covering letter. Authors should list their title and affiliation at the time they did the work, and, if different, their present affiliation. The addresses and telephone numbers of all authors should be supplied for editorial purposes. All authors of a manuscript are responsible for having read and approved it for submission.

CATEGORIES

Research Papers should be limited to 2,500 words and should include the following sections: Introduction, Methods, Results, Discussion, and References. Multiple subheadings and numbered lists are discouraged. An abstract limited to 150 words should state the reasons for the study, the main findings, and their implications. Statistical evaluations should be described in the Methods section, and the name and affiliation of the statistician should be included in the acknowledgments if this individual is not listed as a coauthor. Reports of experiments involving human subjects must include a description in the Methods section of the informed consent obtained and a statement that the procedures followed were approved by an institutional research review committee. Anonymity of patients must be preserved. Reports of experiments on animals must note which guidelines were followed for the care and use of laboratory animals.

Case Reports should be limited to 1,250 words. Review Articles should not exceed 3,000 words. Commentaries should be between 750 and 1,000 words. Other kinds of original essays should not exceed 2,000 words. A letter of inquiry should be sent to the editor prior to submitting a Review Article or Commentary.

For Research Papers only, scientific measurements should be given in conventional units, with Système Internationale (SI) units in parentheses. Abbreviations and acronyms should be kept to a minimum, and jargon should be avoided. Generic names of drugs should be used instead of brand names.

FIGURES

The submission of color illustrations or slides is discouraged. Only black and white glossy photographic prints or "camera-ready" artwork will be accepted. The *Journal* is unable to provide art services such as the addition of arrows to photographs. A signed consent for publication must accompany photographs in which the patient is identifiable. Illustrations from other publications generally will not be considered. Legends for illustrations should be typed on a separate sheet, and for photomicrographs should include magnification and stain. Each illustration should be lightly marked on the back in pencil with the name of the first author, the number as cited in the text, and an arrow indicating the top. Each set of illustrations should be submitted unmounted in a separate envelope.

Tables should be simple, self-explanatory, and few in number. Each table should be typed double-spaced on a separate sheet.

REFERENCES

References should be limited to the most pertinent. The recommended maximum number of references is 25 for Research Papers and most other original contributions (except lengthier Review Articles), 12 for Commentaries and Case Reports, and six for letters to the editor.

Authors are responsible for the accurate citation of references. Citation of secondary sources is discouraged except where the original reference is unobtainable. Authors may not cite references they have not read, and the use of abstracts as references should be avoided.

References should be indicated in the text by superscript numbers following the name of the author (eg, Smith^2 reported two cases).

The list of references at the end of the article should be typed double-spaced and references should be numbered in the order in which they appear on the text. When there are six or fewer authors, all should be listed; where there are seven or more, the first three should be listed, followed by *et al.* Names of journals should be abbreviated according to *Index Medicus* and underlined.

Sample references:

1. Kepes ER, Thomas P, Vemulapalli K: Methadone and intravenous morphine requirements. *NY State J Med* 1983; 83:925-927.
2. McGuigan JE. Peptic ulcer. In: Petersdorf RG, Adams RD, Braunwald E, Isselbacher KJ, Martin JB, Wilson JD, eds. *Harrison's Principles of Internal Medicine.* New York, McGraw-Hill, 1983, pp 1697–1712.

REVIEW

All manuscripts are reviewed by the editors, and most manuscripts are sent to outside referees. Decisions concerning acceptance, revision, or rejection of a manuscript are usually made within three to six weeks. Every effort will be made to assure prompt publication of an accepted manuscript. A galley proof will be sent to the author for approval prior to publication.

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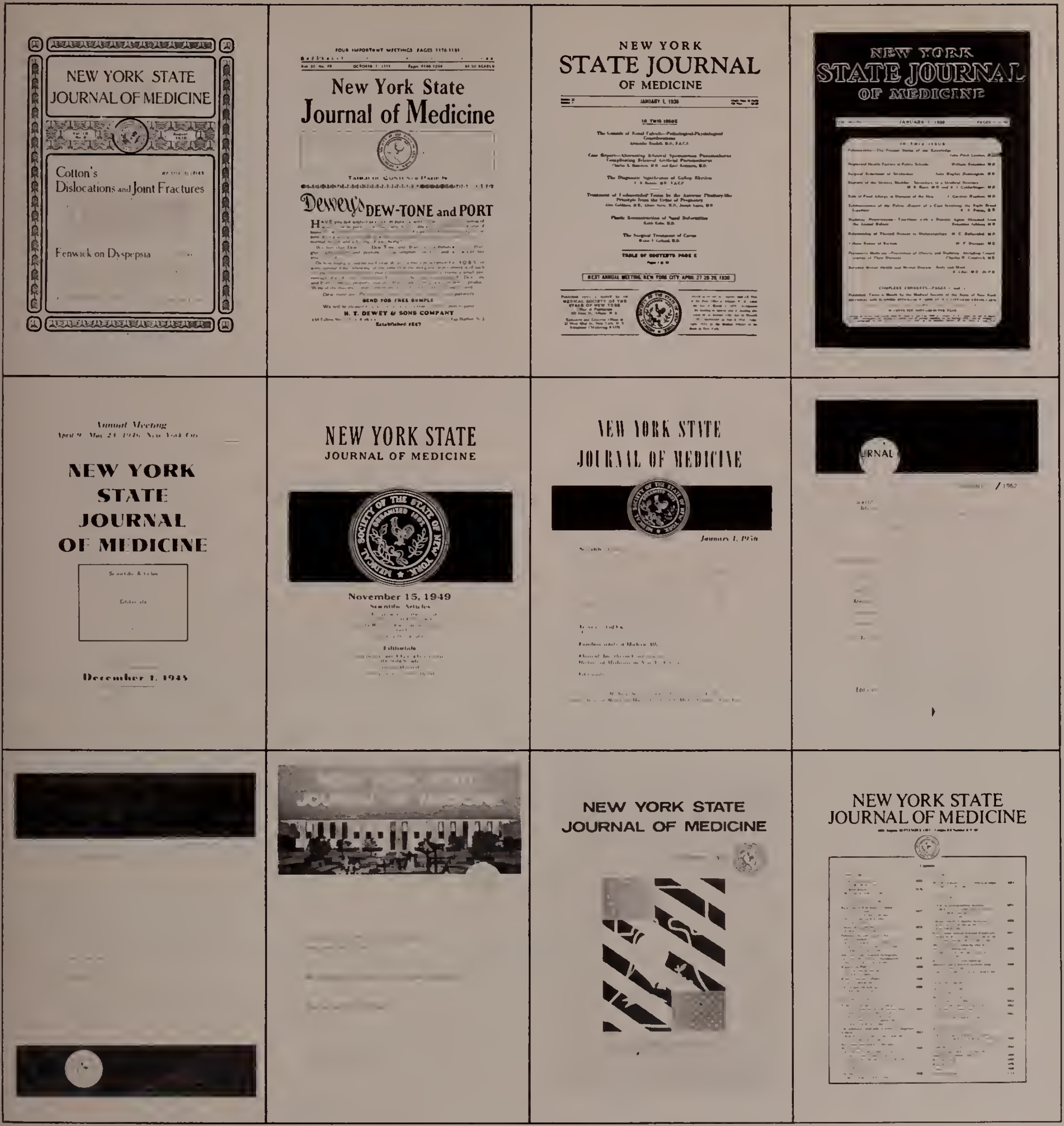
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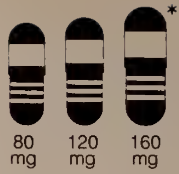

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)*

INDERAL® LA brand of propranolol hydrochloride **(Long Acting Capsules)**

DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.

CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity.

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain.

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma; 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS. CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

> IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)— PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

Just once each day...

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. *General:* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized.* The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily.

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

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Contraindications: Anaphylactoid reactions have occurred in individuals hypersensitive to *Motrin* Tablets or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin, iodides, or other nonsteroidal anti-inflammatory agents.

Warnings: Peptic ulceration and GI bleeding, sometimes severe, have been reported. Ulceration, perforation and bleeding may end fatally. An association has not been established. Use *Motrin* Tablets under close supervision in patients with a history of upper gastrointestinal tract disease, after consulting ADVERSE REACTIONS. In patients with active peptic ulcer and active rheumatoid arthritis, try nonulcerogenic drugs, such as gold. If *Motrin* Tablets are used, observe the patient closely for signs of ulcer perforation or GI bleeding.

Chronic studies in rats and monkeys have shown mild renal toxicity with papillary edema and necrosis. Renal papillary necrosis has rarely been shown in humans treated with *Motrin* Tablets.

Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue *Motrin* Tablets and the patient should have an ophthalmologic examination, including central visual fields and color vision testing.

Fluid retention and edema have been associated with *Motrin* Tablets; use with caution in patients with a history of cardiac decompensation or hypertension. In patients with renal impairment, reduced dosage may be necessary. Prospective studies of *Motrin* Tablets safety in patients with chronic renal failure have not been done.

Motrin Tablets can inhibit **platelet aggregation** and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and on anticoagulant therapy.

Patients should report signs or symptoms of **gastrointestinal ulceration** or bleeding, skin rash, weight gain, or edema.

Patients on prolonged **corticosteroid therapy** should have therapy tapered slowly when *Motrin* Tablets are added.

The antipyretic, anti-inflammatory activity of *Motrin* Tablets may mask inflammation and fever.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Meaningful elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. If liver disease develops or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), *Motrin* should be discontinued.

Drug interactions. *Aspirin:* used concomitantly may decrease *Motrin* blood levels.

Coumarin: bleeding has been reported in patients taking *Motrin* and coumarin.

Pregnancy and nursing mothers: *Motrin* should not be taken during pregnancy or by nursing mothers.

Adverse Reactions: The most frequent type of adverse reaction occurring with *Motrin* is gastrointestinal of which one or more occurred in 4% to 16% of the patients.

Incidence Greater than 1% (but less than 3%)—Probable Causal Relationship

Gastrointestinal: Nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence); **Central Nervous System:** Dizziness,* headache, nervousness; **Dermatologic:** Rash* (including maculopapular type), pruritus; **Special Senses:** Tinnitus; **Metabolic/Endocrine:** Decreased appetite; **Cardiovascular:** Edema, fluid retention (generally responds promptly to drug discontinuation; see PRECAUTIONS).

*Incidence less than 1%—Probable Causal Relationship***

Gastrointestinal: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; **Central Nervous System:** Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia; **Special Senses:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata, and/or changes in color vision) (see PRECAUTIONS); **Hematologic:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit, **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; **Allergic:** Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis; bronchospasm (see CONTRAINDICATIONS); **Renal:** Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; **Miscellaneous:** Dry eyes and mouth, gingival ulcer, rhinitis.

*Incidence less than 1%—Causal Relationship Unknown***

Gastrointestinal: Pancreatitis; **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; **Dermatologic:** Toxic epidermal necrolysis, photoallergic skin reactions; **Special Senses:** Conjunctivitis, diplopia, optic neuritis; **Hematologic:** Bleeding episodes (e.g., epistaxis, menorrhagia); **Metabolic/Endocrine:** Gynecomastia, hypoglycemic reaction; **Cardiovascular:** Arrhythmias (sinus tachycardia, sinus bradycardia); **Allergic:** Serum sickness, lupus erythematosus syndrome, Henoch-Schonlein vasculitis; **Renal:** Renal papillary necrosis.

*Reactions occurring in 3% to 9% of patients treated with *Motrin*. (Those reactions occurring in less than 3% of the patients are unmarked.)

**Reactions are classified under *"Probable Causal Relationship (PCR)"* if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under *"Causal Relationship Unknown"* if seven or more events have been reported but the criteria for PCR have not been met.

Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine so alkaline diuresis may be beneficial.

Dosage and Administration: Rheumatoid arthritis and osteoarthritis. Suggested dosage is 300, 400, or 600 mg t.i.d. or q.i.d. Do not exceed 2400 mg per day. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary.

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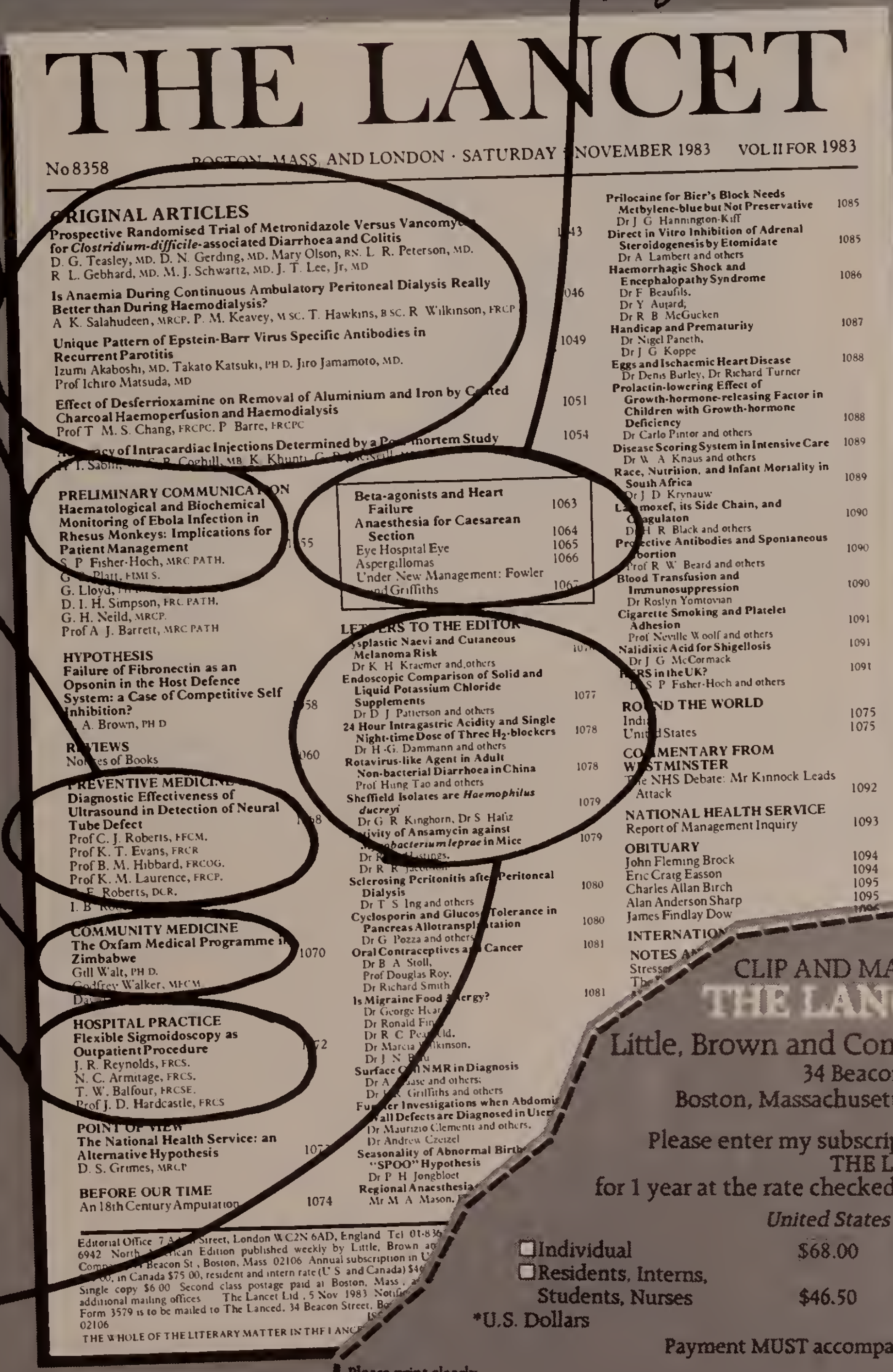

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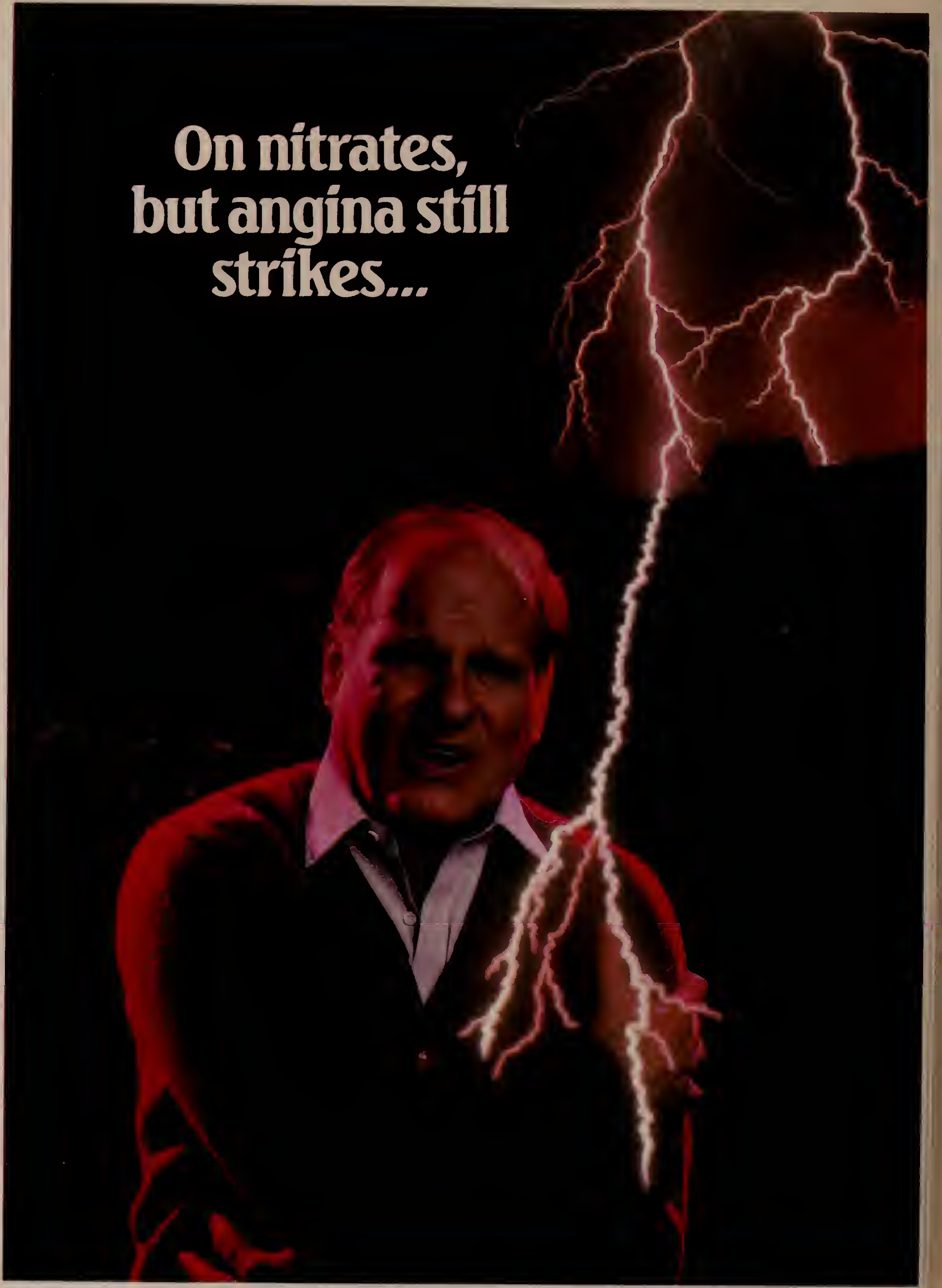
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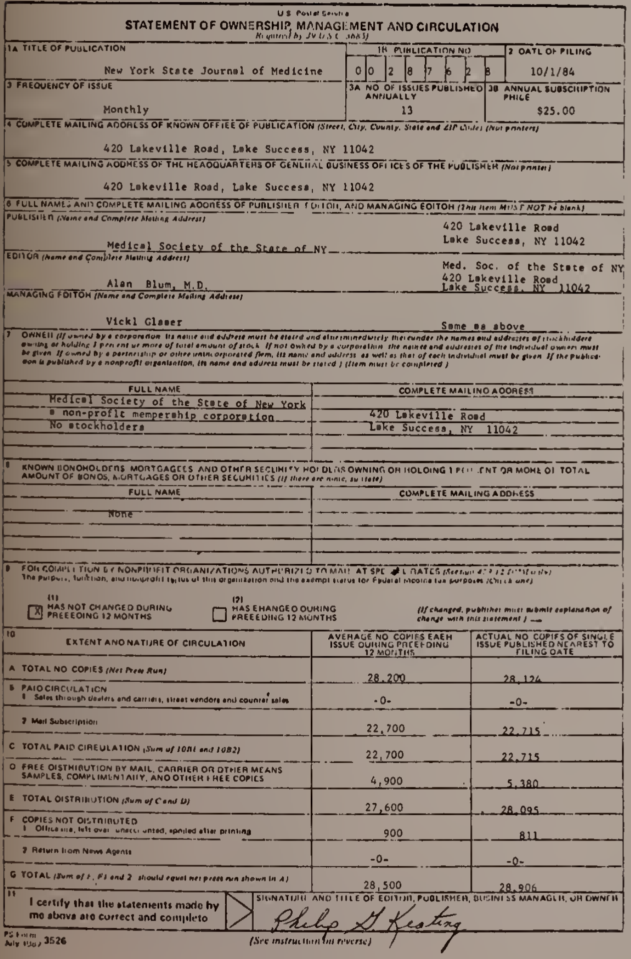

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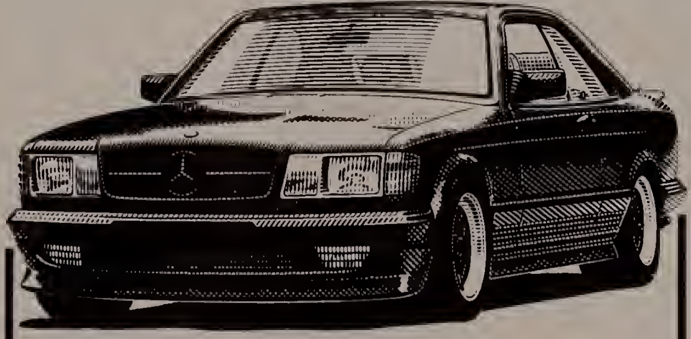

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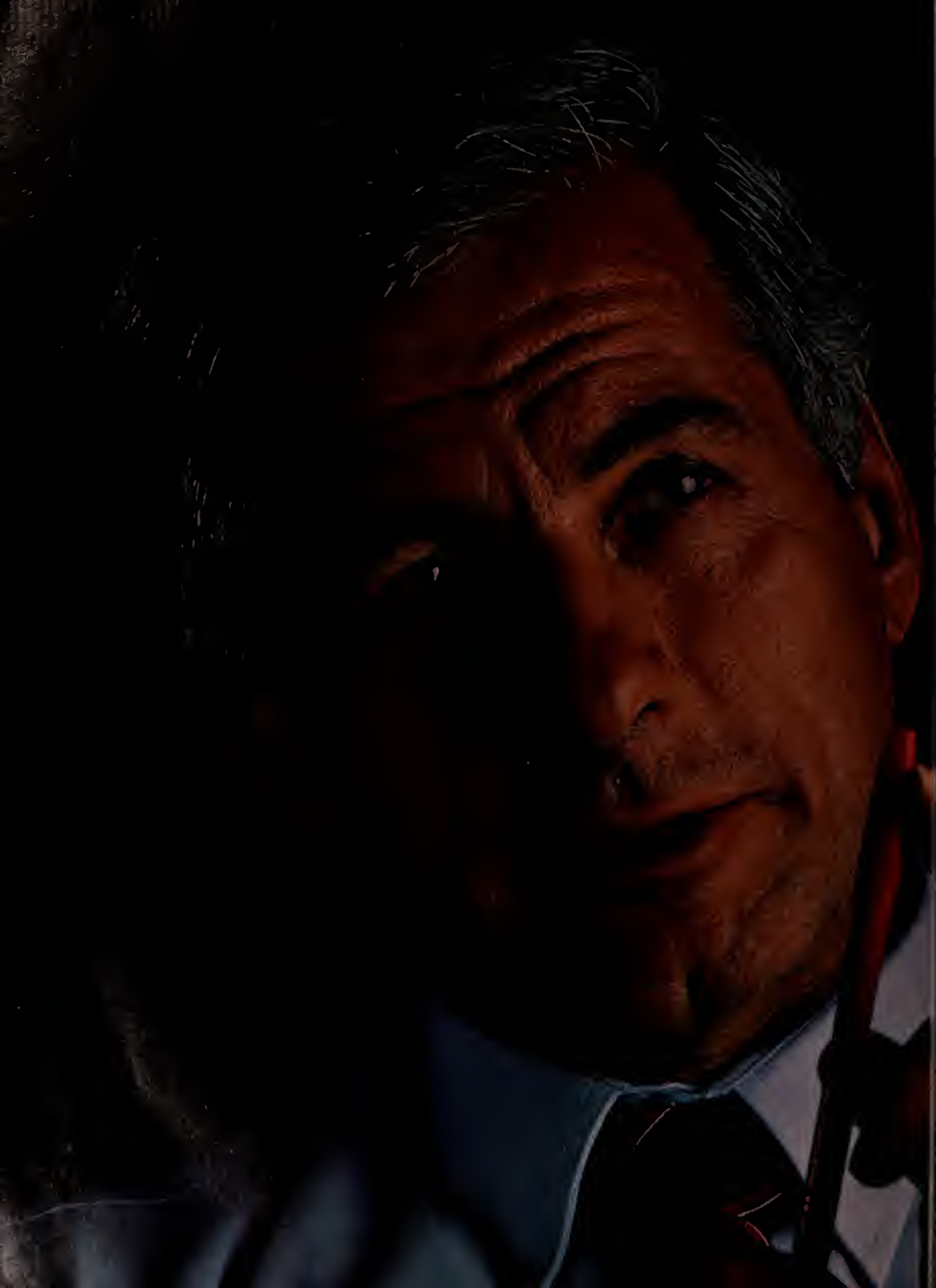

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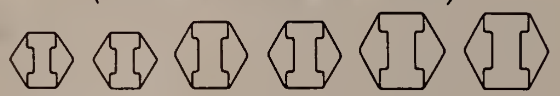

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Although the clinical trials used either t.i.d. or q.i.d. dosing, clinical, pharmacologic and pharmacokinetic data provide a reasonable basis for concluding that b.i.d. dosing with propranolol should be adequate in the treatment of post-infarction patients.

CLINICAL: In the BHAT, patients on INDERAL were prescribed either 180 mg/day (82% of patients) or 240 mg/day (18% of patients). Patients were instructed to take the medication 3 times a day at mealtimes. This dosing schedule would result in an overnight dosing interval of 12 to 14 hours which is similar to the dosing interval for a b.i.d. regimen. In addition, blood samples were drawn at various times and analyzed for propranolol. When the patients were grouped into tertiles based on the blood levels observed and the mortality in the upper and lower tertiles were compared, there was no evidence that blood levels affected mortality.

PHARMACOLOGIC: Studies in normal volunteers have shown that a 90 mg b.i.d. regimen maintains beta blockade at, or above, the minimum for 60 mg t.i.d. dosing for 24 hours even though differences occurred at two time intervals. At 10-12 hours after the first dose of the day, t.i.d. dosing gave more beta blockade than b.i.d. dosing; at 20-24 hours the trend of the relationship was reversed. These relationships were similar in direction to those observed for plasma propranolol levels (see Pharmacokinetic).

PHARMACOKINETIC: A bioavailability study in normal volunteers showed that the blood levels produced by 180 mg/day given b.i.d. are below those provided by the same daily dosage given t.i.d. at 10-12 hours after the first dose of the day but above those of a t.i.d. regimen at 20-24 hours. However, the blood levels produced by b.i.d. dosing were always equivalent to or above the minimum for t.i.d. dosing throughout the 24 hours. In addition, the mean AUC on the fourth day for the b.i.d. regimen was about 17% greater than for the t.i.d. regimen (1,194 vs. 1,024 ng/ml·hr).

CONTRAINDICATIONS

INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS

CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

> IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL (propranolol hydrochloride) should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS

General: Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia; congestive heart failure, intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

*The appearance of INDERAL tablets is a registered trademark of Ayerst Laboratories.

9371/1184

Ayerst®
AYERST LABORATORIES
New York, N.Y. 10017

BALANCED CALCIUM CHANNEL BLOCKADE!

CARDIZEM®
(diltiazem HCl)
balances potent coronary vasodilation with a low incidence of side effects

Low incidence of side effects
CARDIZEM® (diltiazem HCl) produces an incidence of adverse reactions not greater than that reported with placebo therapy, thus contributing to the patient's sense of well-being.

Reduces angina attack frequency*
42% to 46% decrease reported in multicenter study.[1]

Increases exercise tolerance*
In Bruce exercise test,[2] control patients averaged 8.0 minutes to onset of pain; Cardizem patients averaged 9.8 minutes ($P<.005$).

CARDIZEM®
(diltiazem HCl)

THE BALANCED CALCIUM CHANNEL BLOCKER

Please see full prescribing information on following page. 2/84

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*Cardizem is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

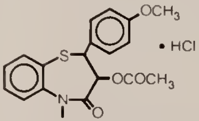
References:
1. Strauss WE, McIntyre KM, Parisi AF, et al: Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris: Report of a cooperative clinical trial. Am J Cardiol 49:560-566, 1982.
2. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. Chest 78 (July suppl):234-236, 1980.

PROFESSIONAL USE INFORMATION

cardizem®
(diltiazem HCl)
30 mg and 60 mg tablets

DESCRIPTION

CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+)-cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem hydrochloride for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CAROIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina. CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIONS and ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS).

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%), AV block (1.1%). In addition, the following events were reported infrequently (less than 1%) with the order of presentation corresponding to the relative frequency of occurrence.

Cardiovascular:	Flushing, arrhythmia, hypotension, bradycardia, palpitations, congestive heart failure, syncope.
Nervous System:	Paresthesia, nervousness, somnolence, tremor, insomnia, hallucinations, and amnesia.
Gastrointestinal:	Constipation, dyspepsia, diarrhea, vomiting, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH.
Dermatologic:	Pruritus, petechiae, urticaria, photosensitivity.
Other:	Polyuria, nocturia.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: erythema multiforme; leukopenia; and extreme elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK. However, a definitive cause and effect between these events and CAROIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been limited. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Oegree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral/LO$_{50}$'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LO$_{50}$'s in these species were 60 and 38 mg/kg, respectively. The oral LD$_{50}$ in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. Although individual patients may respond to any dosage level, the average optimum dosage range appears to be 180 to 240 mg/day. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

Cardizem 30-mg tablets are supplied in bottles of 100 (NOC 0088-1771-47) and in Unit Dose Identification Paks of 100 (NOC 0088-1771-49). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NOC 0088-1772-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1772-49). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

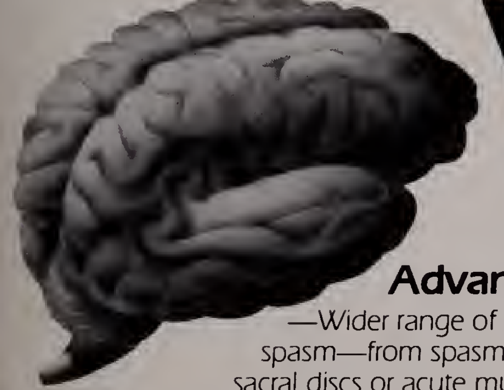
Issued 4/1/84

Another patient benefit product from

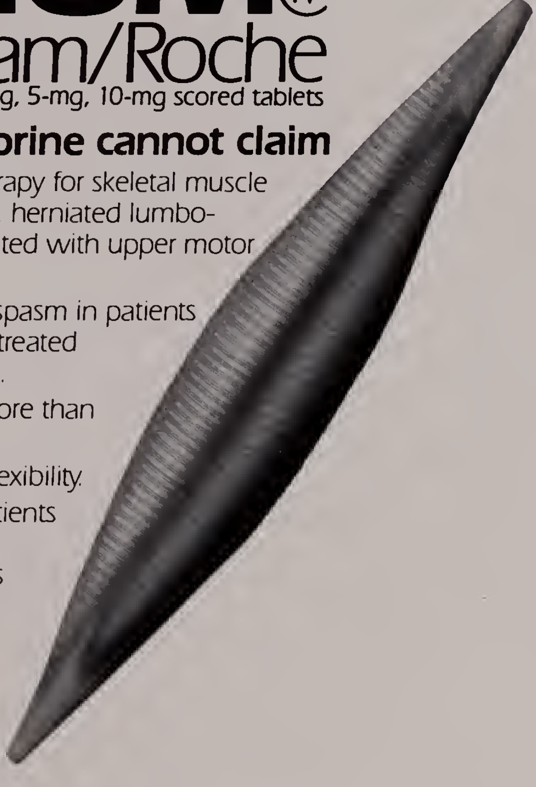
PHARMACEUTICAL DIVISION
MARION
LABORATORIES, INC.
KANSAS CITY, MISSOURI 64137

THE SPASM/PAIN/SPASM CYCLE

In skeletal muscle spasm due to local pathology, responsive to the distinct actions of



Adjunctive
VALIUM® Ⓒ
diazepam/Roche
2-mg, 5-mg, 10-mg scored tablets



Advantages cyclobenzaprine cannot claim

—Wider range of indications as adjunctive therapy for skeletal muscle spasm—from spasm due to local pathology (*e.g.*, herniated lumbosacral discs or acute muscle strain) to spasm associated with upper motor neuron disorders (*e.g.*, cerebral palsy and paraplegia).

—May be used adjunctively for relieving skeletal muscle spasm in patients with hyperthyroidism, cardiac patients and patients being treated with anticholinergics or guanethidine-type antihypertensives.

—Can be administered to patients less than 15 years and more than 6 months of age.

—Scored tablets in three strengths provide greater dosage flexibility.

Since drowsiness, fatigue and ataxia sometimes occur, patients should be cautioned against driving or operating hazardous machinery and should also be advised against simultaneous ingestion of alcohol.

References: 1. Rankin EA: *Contin Educ 3*(1):46-50, Jan 1975. **2.** When muscle spasm hobbles your patient. *Patient Care 8*(11):20-37, Jun 1, 1974.

Valium® (diazepam/Roche) Ⓒ
Before prescribing, please consult complete product information, a summary of which follows:
Indications: Management of anxiety disorders, or short-term relief of symptoms of anxiety Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic Symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal, adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not as sole therapy)
The effectiveness of Valium in long-term use, that is, more than 4 months, has not been assessed by systematic clinical studies The physician should periodically reassess the usefulness of the drug for the individual patient
Contraindicated: Known hypersensitivity to the drug Children under 6 months of age Acute narrow angle glaucoma, may be used in patients with open angle glaucoma who are receiving appropriate therapy
Warnings: Not of value in psychotic patients Caution against hazardous occupations requiring complete mental alertness When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication, abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures Advise against simultaneous ingestion of alcohol and other CNS depressants Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation, usually limited to extended use and excessive doses Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after continuous use, generally at higher therapeutic levels, for at least several months After extended therapy, gradually taper dosage Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence

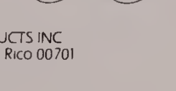
> ***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed, drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies Observe usual precautions in impaired renal or hepatic function Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation
The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration The clinical significance of this is unclear
Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported, should these occur, discontinue drug Isolated reports of neutropenia, jaundice, periodic blood counts and liver function tests advisable during long-term therapy
Dosage: Individualize for maximum beneficial effect *Adults* Anxiety disorders, symptoms of anxiety, 2 to 10 mg b.i.d to q.i.d., alcoholism, 10 mg t.i.d or q.i.d in first 24 hours, then 5 mg t.i.d or q.i.d as needed, adjunctively in skeletal muscle spasm, 2 to 10 mg t.i.d or q.i.d., adjunctively in convulsive disorders, 2 to 10 mg b.i.d. to q.i.d *Geriatric or debilitated patients* 2 to 2½ mg, 1 or 2 times daily initially, increasing as needed and tolerated (See Precautions.) *Children.* 1 to 2½ mg t.i.d. or q.i.d initially, increasing as needed and tolerated (not for use under 6 months)
How Supplied: For oral administration, round, scored tablets with a cut out "V" design—2 mg, white, 5 mg, yellow, 10 mg, blue— bottles of 100 and 500, Prescription Paks of 50, available in trays of 10. Tel-E-Dose® packages of 100, available in boxes of 4 reverse-numbered cards of 25, and in boxes containing 10 strips of 10

Imprint on tablets
2 mg—2 VALIUM® (front)
ROCHE (scored side)

5 mg—5 VALIUM® (front)
ROCHE (scored side)

10 mg—10 VALIUM® (front)
ROCHE (scored side)



ROCHE®
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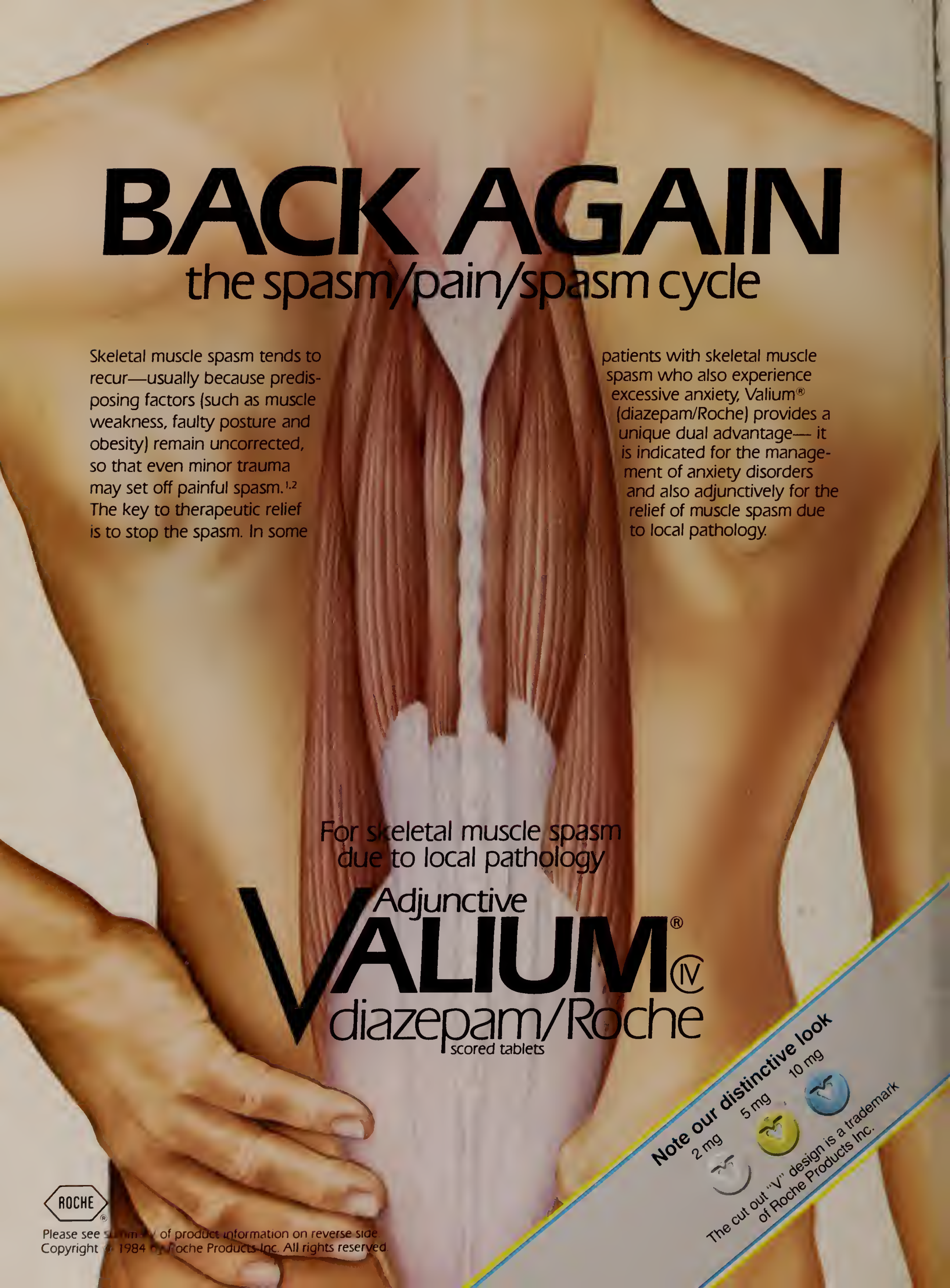

BACK AGAIN

the spasm/pain/spasm cycle

Skeletal muscle spasm tends to recur—usually because predisposing factors (such as muscle weakness, faulty posture and obesity) remain uncorrected, so that even minor trauma may set off painful spasm.[1,2] The key to therapeutic relief is to stop the spasm. In some patients with skeletal muscle spasm who also experience excessive anxiety, Valium® (diazepam/Roche) provides a unique dual advantage— it is indicated for the management of anxiety disorders and also adjunctively for the relief of muscle spasm due to local pathology.

For skeletal muscle spasm due to local pathology

Adjunctive

VALIUM® Ⓘⓥ

diazepam/Roche

scored tablets

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NEW YORK STATE JOURNAL OF MEDICINE

DECEMBER 1984 • Volume 84, Number 12

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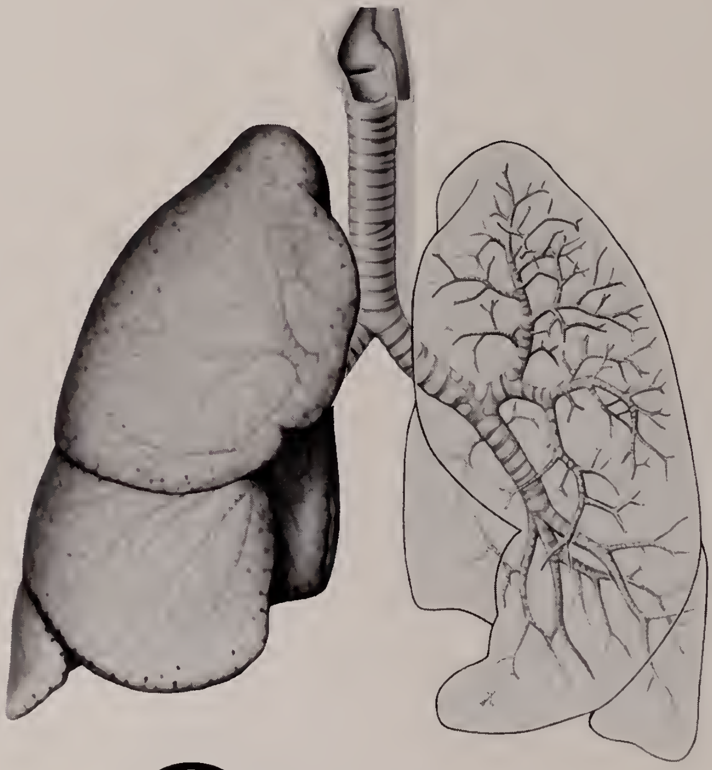
Consider the causative organisms…



Ceclor®
cefaclor

250-mg Pulvules® t.i.d.

offers effectiveness against the major causes of bacterial bronchitis

H. influenzae, (ampicillin-susceptible) *H. influenzae*, (ampicillin-resistant) *S. pneumoniae*, *S. pyogenes*

Brief Summary Consult the package literature for prescribing information

Indications and Usage Ceclor* (cefaclor Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms

Lower respiratory infections including pneumonia caused by *Streptococcus pneumoniae (Diplococcus pneumoniae)*, *Haemophilus influenzae* and *S pyogenes* (group A beta-hemolytic streptococci)

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor

Contraindication Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics

Warnings IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES

Antibiotics including Ceclor should be administered cautiously to any patient who has demonstrated some form of allergy particularly to drugs

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins), therefore it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics Such colitis may range in severity from mild to life-threatening

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation When the colitis does not improve after the drug has been discontinued, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by C *difficile* Other causes of colitis should be ruled out

Precautions *General Precautions* — If an allergic reaction to Ceclor* (cefaclor, Lilly) occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e g pressor amines, antihistamines, or corticosteroids

Prolonged use of Ceclor may result in the overgrowth of nonsusceptible organisms Careful observation of the patient is essential If superinfection occurs during therapy, appropriate measures should be taken

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug

Ceclor should be administered with caution in the presence of markedly impaired renal function Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur This has been observed with Benedict's and Fehling's solutions and also with Clinitest* tablets but not with Tes-Tape* (Glucose Enzymatic Test Strip, USP, Lilly)

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis

Usage in Pregnancy — Pregnancy Category B — Reproduction studies have been performed in mice and rats at doses up to 12 times the human dose and in ferrets given three times the maximum human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Ceclor* (cefaclor, Lilly) There are, however, no adequate and well-controlled studies in pregnant women Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Nursing Mothers — Small amounts of Ceclor have been detected in mother's milk following administration of single 500-mg doses Average levels were 0 18, 0 20, 0 21, and 0 16 mcg/ml at two, three, four, and five hours respectively Trace amounts were detected at one hour The effect on nursing infants is not known Caution should be exercised when Ceclor is administered to a nursing woman

Usage in Children — Safety and effectiveness of this product for use in infants less than one month of age have not been established

Adverse Reactions Adverse effects considered related to therapy with Ceclor are uncommon and are listed below

Gastrointestinal symptoms occur in about 2 5 percent of patients and include diarrhea (1 in 70).

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely

Hypersensitivity reactions have been reported in about 1 5 percent of patients and include morbilliform eruptions (1 in 100) Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever) have been reported These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Ceclor Such reactions have been reported more frequently in children than in adults Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy No serious sequelae have been reported Antihistamines and corticosteroids appear to enhance resolution of the syndrome

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients)

Causal Relationship Uncertain — Transitory abnormalities in clinical laboratory test results have been reported Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician

Hepatic — Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40)

Hematopoietic — Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40)

Renal — Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200)

[0617B2R]

Note Ceclor* (cefaclor, Lilly) is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever See prescribing information

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BALANCED CALCIUM CHANNEL BLOCKADE!

CARDIZEM
(diltiazem HCl)
balances potent coronary vasodilation with a low incidence of side effects

Low incidence of side effects
CARDIZEM® (diltiazem HCl) produces an incidence of adverse reactions not greater than that reported with placebo therapy, thus contributing to the patient's sense of well-being.

*Cardizem is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

References:

1. Strauss WE, McIntyre KM, Parisi AF, et al: Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris: Report of a cooperative clinical trial. Am J Cardiol 49:560-566, 1982.
2. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. Chest 78 (July suppl):234-238, 1980.

Reduces angina attack frequency*
42% to 46% decrease reported in multicenter study.[1]

Increases exercise tolerance*
In Bruce exercise test,[2] control patients averaged 8.0 minutes to onset of pain; Cardizem patients averaged 9.8 minutes ($P<.005$).

CARDIZEM®
(diltiazem HCl)

THE BALANCED CALCIUM CHANNEL BLOCKER

Please see full prescribing information on following page.

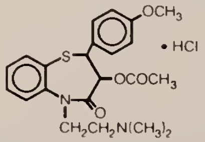
2/84

PROFESSIONAL USE INFORMATION

cardizem®
(diltiazem HCl)
30 mg and 60 mg tablets

DESCRIPTION

CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+)-cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem hydrochloride for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina. CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIONS and ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS).

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%), AV block (1.1%). In addition, the following events were reported infrequently (less than 1%) with the order of presentation corresponding to the relative frequency of occurrence.

Cardiovascular:	Flushing, arrhythmia, hypotension, bradycardia, palpitations, congestive heart failure, syncope.
Nervous System:	Paresthesia, nervousness, somnolence, tremor, insomnia, hallucinations, and amnesia.
Gastrointestinal:	Constipation, dyspepsia, diarrhea, vomiting, mild elevations of alkaline phosphatase, SGDT, SGPT, and LDH.
Dermatologic:	Pruritus, petechiae, urticaria, photosensitivity.
Other:	Polyuria, nocturia.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: erythema multiforme; leukopenia; and extreme elevations of alkaline phosphatase, SGDT, SGPT, LDH, and CPK. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been limited. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral/LD$_{50}$'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD$_{50}$'s in these species were 60 and 38 mg/kg, respectively. The oral LD$_{50}$ in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. Although individual patients may respond to any dosage level, the average optimum dosage range appears to be 180 to 240 mg/day. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

Cardizem 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1771-49). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1772-49). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

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Experience no other beta blocker can match... Once-daily INDERAL LA delivers the proven performance and safety profile of INDERAL tablets—confirmed by millions of patients during 16 years of clinical use. INDERAL LA should not be used in congestive heart failure, sinus bradycardia, heart block greater than first degree, or bronchial asthma.

Start with 80 mg once daily... Dosage may be increased to 120 mg or 160 mg once daily as needed to achieve additional control. Please see next page for further details and brief summary of prescribing information.

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INDERAL LA

(PROPRANOLOL HCl) LONG-ACTING CAPSULES

Just once each day for initial therapy in hypertension.

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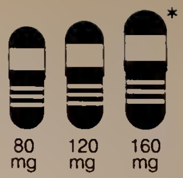

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)*
INDERAL® LA brand of propranolol hydrochloride **(Long Acting Capsules)**

DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.

CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces th[illegible]n re[illegible]t any given level of effort by blocking the catecholamine-[illegible]d inc[illegible] the h[illegible] rate, systolic blood pressure, and the velocity and extent of [illegible]dial [illegible]nolol may increase oxygen requirements by increasing left [illegible]lar f[illegible] length, [illegible]stolic pressure and systolic ejection period. The net phy[illegible]ener[illegible]de is usually advantageous and is manifested duri[illegible]rcis[illegible]nd increased work capacity

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine- or anesthetic-like membrane action which affects th[illegible]c a[illegible]nti[illegible]ig[illegible]cance of the membrane action in the treatment of [illegible]ythm[illegible]ce[illegible]

The mechanism of the antimigraine effect of pr[illegible]lishe[illegible]adrenergic receptors have been demonstrated in [illegible]pial ves[illegible] of the [illegible]

Beta receptor blockade can be useful in con[illegible]ns in [illegible] bec[illegible]ath[illegible]r functional changes, sympathetic activity is detri[illegible]u[illegible]so situations in which sympathetic stimulation is vital. F[illegible] exampl[illegible] in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first degree block; 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS. CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

> IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers

DIABETES AND HYPOGLYCEMIA: Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker In one case this resulted after an initial dose of 5 mg propranolol

PRECAUTIONS. *General:* Propranolol should be used with caution in patients with impaired hepatic or renal function INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure Patients should be told that INDERAL may interfere with the glaucoma screening test Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in [illegible]rats [illegible] empl[illegible]oses [illegible] 150 mg/kg/day, there was no evidence of significant [illegible]lated tumorigenic effects at any of the dosage levels [illegible]duc[illegible]dies [illegible]mals [illegible] not show any impairment of fertility that was attrib[illegible] to th[illegible]

[illegible]ncy: [illegible]ncy C[illegible]ry C. INDERAL has been shown to be embryotoxic in [illegible]ies a[illegible]er than the maximum recommended human dose. Th[illegible] are n[illegible]eq[illegible]d w[illegible]olled studies in pregnant women INDERAL should be used during [illegible]gnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mot[illegible]s: INDERAL is excreted in human milk Caution should be exercised when [illegible]DERAL [illegible]d[illegible]ste[illegible] a [illegible]rsing woman.

Pe[illegible]ric [illegible]ely a[illegible]ctive[illegible]ss in children have not been established

[illegible]OV[illegible]SE R[illegible]CTIONS [illegible] ad[illegible]se effects have been mild and transient and have [illegible]rely [illegible]quired [illegible]draw[illegible] of [illegible]er[illegible]y

C[illegible]diovas[illegible] [illegible]brady[illegible]dia [illegible]gestive heart failure; intensification of AV block, hypo[illegible]nsio[illegible]s[illegible] thr[illegible]bo[illegible]urpura, arterial insufficiency, usually of the [illegible]aynaud type.

Central Nervous System: [illegible]headedness; mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia, visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval

HYPERTENSION—*Dosage must be individualized* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved The usual maintenance dosage is 120 to 160 mg once daily In some instances a dosage of 640 mg may be required The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks

ANGINA PECTORIS—*Dosage must be individualized* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized* The initial oral dose is 80 mg INDERAL LA once daily The usual effective dose range is 160-240 mg once daily The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use

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FAMILY PHYSICIAN—Northeastern New York Board Family Physician wanted to join active, private, group practice of family medicine, all board certified family physicians, including obstetrics and hospital care in an excellent local community hospital. Suburban Albany area. Contact: Business Manager 1-(518) 785-4471.

OBSTETRICIAN & GYNECOLOGIST, Southern California-Leading HMO with 28 facilities, 350,000 members and 370 full-time physicians in Los Angeles and Orange Counties has opportunities for OB/GYN specialists. Excellent compensation and benefits. Send curriculum vitae to Director/Physician Recruitment: CIGNA Healthplans of California, 700 N. Brand Blvd., Suite 500, Glendale, CA 91203.

WANTED: INTERNIST CARDIOLOGIST. Must be board certified or eligible City of 25,000 in beautiful Upstate New York. Excellent 200 bed local hospital a ½ block away. Small group with large practice, well established for 40 years. Permanent placement. Complete in-house clinical lab, x-ray and physical fitness lab. Opening must be filled by July 1, 1985. Send CV to 110 No. Main St., Cortland, New York 13045.

PHYSICIAN DURING JULY AND AUGUST 1985 for children's camp located at Beach Lake, PA. accommodates 350 campers, ages 6–16; complete modern Health Center; 2 R.N.'s in attendance; will accept one M.D. for each month; no children accepted who are of camp age. Camp opens June 29 and closes August 23. Private room and facilities. Write (and include your phone number) to Trail's End Camp, c/o Beach Lake, Inc., 215 Adams Street, Brooklyn, NY 11201.

SEMI-RETIRED INTERNIST OR GP to join a busy Internist in Upstate New York largely office based practice needed in February 1985. Send CV to Dept. 371, c/o NYSJM.

WANTED: GENERAL INTERNIST to join well established Board Certified Internist with special interest in Diagnostic Cardiology in Rochester, NY. Well equipped office with X-Ray E.K.G.'s. Affiliated with University Hospital in a busy section with population over 100,000. Reply A. Pirincci, M.D., 3000 Mount Read Blvd., Rochester, NY 14616 or call (716) 865-3223.

PHARMACOLOGIST

Researches & analyses effects of drugs, gases, dusts, etc. on discrete tissues and cells and on physiological processes of animals and humans. Experiments with whole animals, isolated organs, cell pop and purified enzymes.

Ph.D. Human Physiology and Pharmacology, 3 years postdoc research, familiarity with biochem pharmacology of arachidonic acid metabolism in kidneys and physiology of whole organisms, discrete organs, cell pops and enzymes.

Must know mass spectrometry and thin layer, high performance liquid, and gas or chromatography, and techniques of dual urinary-vascular bioassay systems and whole organ perfussion for examining hormonal interactions.

40 hour, 5 day week, salary $462.00 per week. Report to NYS Job Service with resume, 55 Church Street, White Plains, NY. Refer to Job order #0740143. DOT code 041.061.074.

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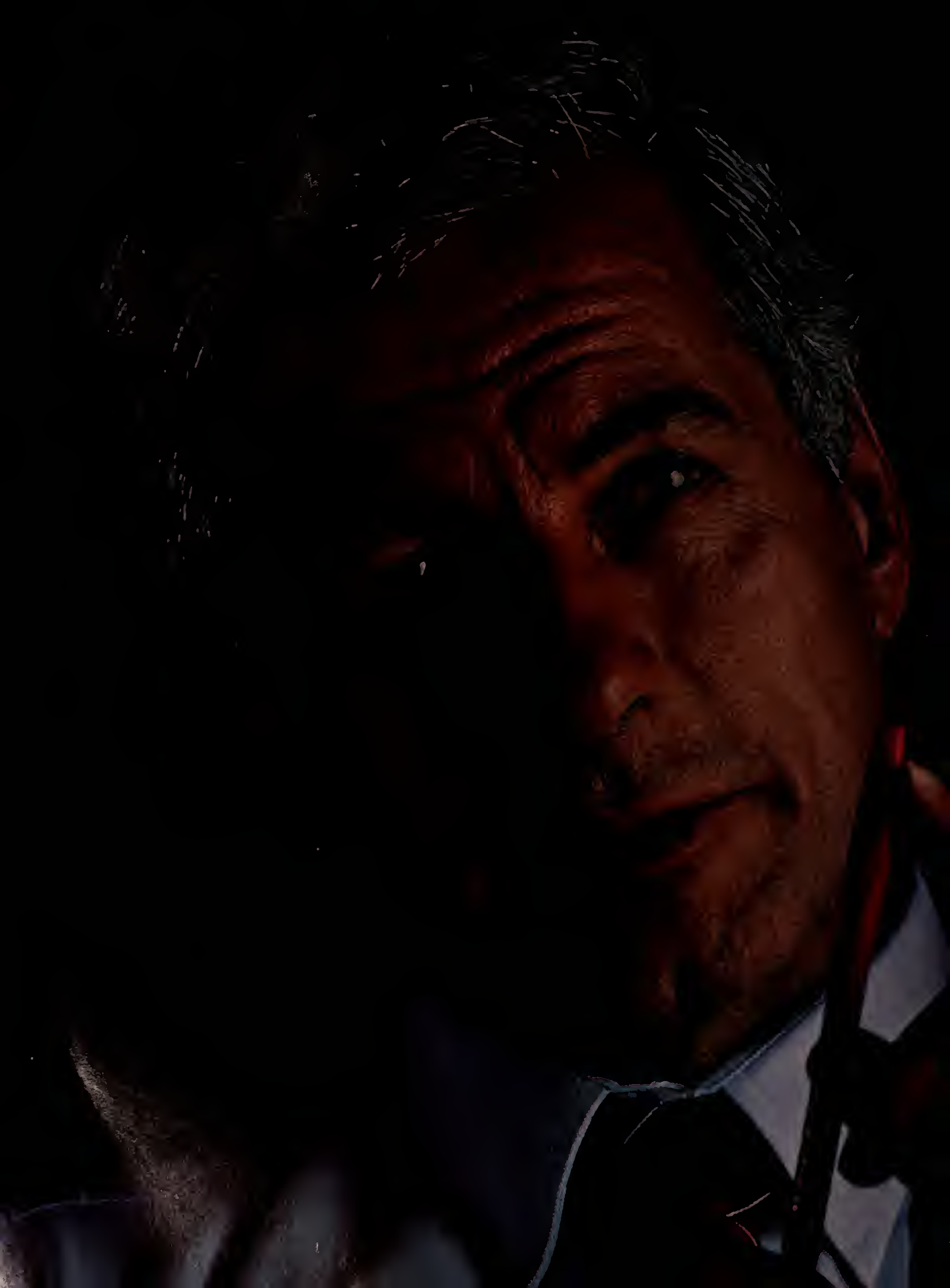
PHYSICIAN FOR CHILDREN'S SUMMER CAMP. Located in lower NYS Catskills, CAMP ECHO seeks Physicians for July and August 1985. Physicains for two or four week periods, with or without camp age children. Excellent medical facility, 2 R.N.'s + aide, private rooms and facilities for M.D. Camp accommodates 350 boys and girls from 6-16 yrs. of age. Write CAMP ECHO, P.O. Box 255, Roslyn, NY 11576 or call (516) 742-2679.

GENERAL/FAMILY PRACTITIONERS, if you are looking for an opportunity to be in the forefront of medical care, practice preventive medicine, work with other innovative professionals, and earn a comfortable living in pleasant surroundings, send your curriculum vitae to Physician Placement Dept.—38. An equal opportunity employer. CIGNA Healthplans of California, 700 N. Brand Blvd., Suite 500, Glendale, CA 91203.

OBSTETRICIAN/GYNECOLOGIST: Second OB/GYN needed to join this rural group practice of 10 physicians. Primary care is emphasized. Formal tertiary linkages to Rochester General Hospital for high risk. Base salary, then income tied to productivity. Contact: Richard F. Endres, M.D., Sodus Health Center, P.O. Box A, Sodus, NY 14551. EOE.



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it costs about 45¢ a day,
I said you can stop right there.”

Most doctors are pleasantly surprised to learn that the average cost of daily therapy with the world’s most widely used beta blocker is so little, not much more than the cost of a daily newspaper.

When it’s INDERAL tablets (propranolol hydrochloride) you want for your hypertension patients, remember to specify Dispense As Written (DAW) or Do Not Substitute on your prescriptions. That way, you can always be assured they’ll get INDERAL®.

Please see next page for brief summary of prescribing information.

INDERAL®
(PROPRANOLOL HCl)
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INDERAL® *TABLETS*

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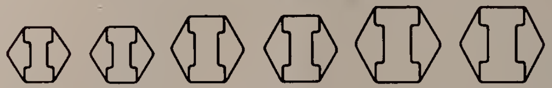

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)

INDERAL® (propranolol hydrochloride) Tablets

CLINICAL PHARMACOLOGY

The Beta-Blocker Heart Attack Trial (BHAT) was a National Heart, Lung and Blood Institute-sponsored multicenter, randomized, double-blind placebo-controlled trial conducted in 31 U.S. centers (plus one in Canada) in 3,837 persons without history of severe congestive heart failure or presence of recent heart failure; certain conduction defects; angina since infarction, who had survived the acute phase of myocardial infarction. Propranolol was administered at either 60 or 80 mg t.i.d. based on blood levels achieved during an initial trial of 40 mg t.i.d. Therapy with INDERAL, begun 5-21 days following infarction, was shown to reduce overall mortality up to 39 months, the longest period of follow-up. This was primarily attributable to a reduction in cardiovascular mortality. The protective effect of INDERAL was consistent regardless of age, sex or site of infarction. Compared to placebo, total mortality was reduced 39% at 12 months and 26% over an average follow-up period of 25 months. The Norwegian Multicenter Trial in which propranolol was administered at 40 mg q.i.d. gave overall results which support the findings in the BHAT.

Although the clinical trials used either t.i.d. or q.i.d. dosing, clinical, pharmacologic and pharmacokinetic data provide a reasonable basis for concluding that b.i.d dosing with propranolol should be adequate in the treatment of post-infarction patients.

CLINICAL: In the BHAT, patients on INDERAL were prescribed either 180 mg/day (82% of patients) or 240 mg/day (18% of patients). Patients were instructed to take the medication 3 times a day at mealtimes. This dosing schedule would result in an overnight dosing interval of 12 to 14 hours which is similar to the dosing interval for a b.i.d. regimen. In addition, blood samples were drawn at various times and analyzed for propranolol. When the patients were grouped into tertiles based on the blood levels observed and the mortality in the upper and lower tertiles were compared, there was no evidence that blood levels affected mortality.

PHARMACOLOGIC: Studies in normal volunteers have shown that a 90 mg b.i.d. regimen maintains beta blockade at, or above, the minimum for 60 mg t.i.d. dosing for 24 hours even though differences occurred at two time intervals. At 10-12 hours after the first dose of the day, t.i.d. dosing gave more beta blockade than b.i.d. dosing, at 20-24 hours the trend of the relationship was reversed These relationships were similar in direction to those observed for plasma propranolol levels (see Pharmacokinetic).

PHARMACOKINETIC: A bioavailability study in normal volunteers showed that the blood levels produced by 180 mg/day given b.i.d are below those provided by the same daily dosage given t.i.d. at 10-12 hours after the first dose of the day but above those of a t.i.d. regimen at 20-24 hours. However, the blood levels produced by b.i.d. dosing were always equivalent to or above the minimum for t.i.d. dosing throughout the 24 hours. In addition, the mean AUC on the fourth day for the b.i.d. regimen was about 17% greater than for the t.i.d. regimen (1,194 vs. 1,024 ng/ml·hr).

CONTRAINDICATIONS

INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS

CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

> IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL (propranolol hydrochloride) should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS

General: Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

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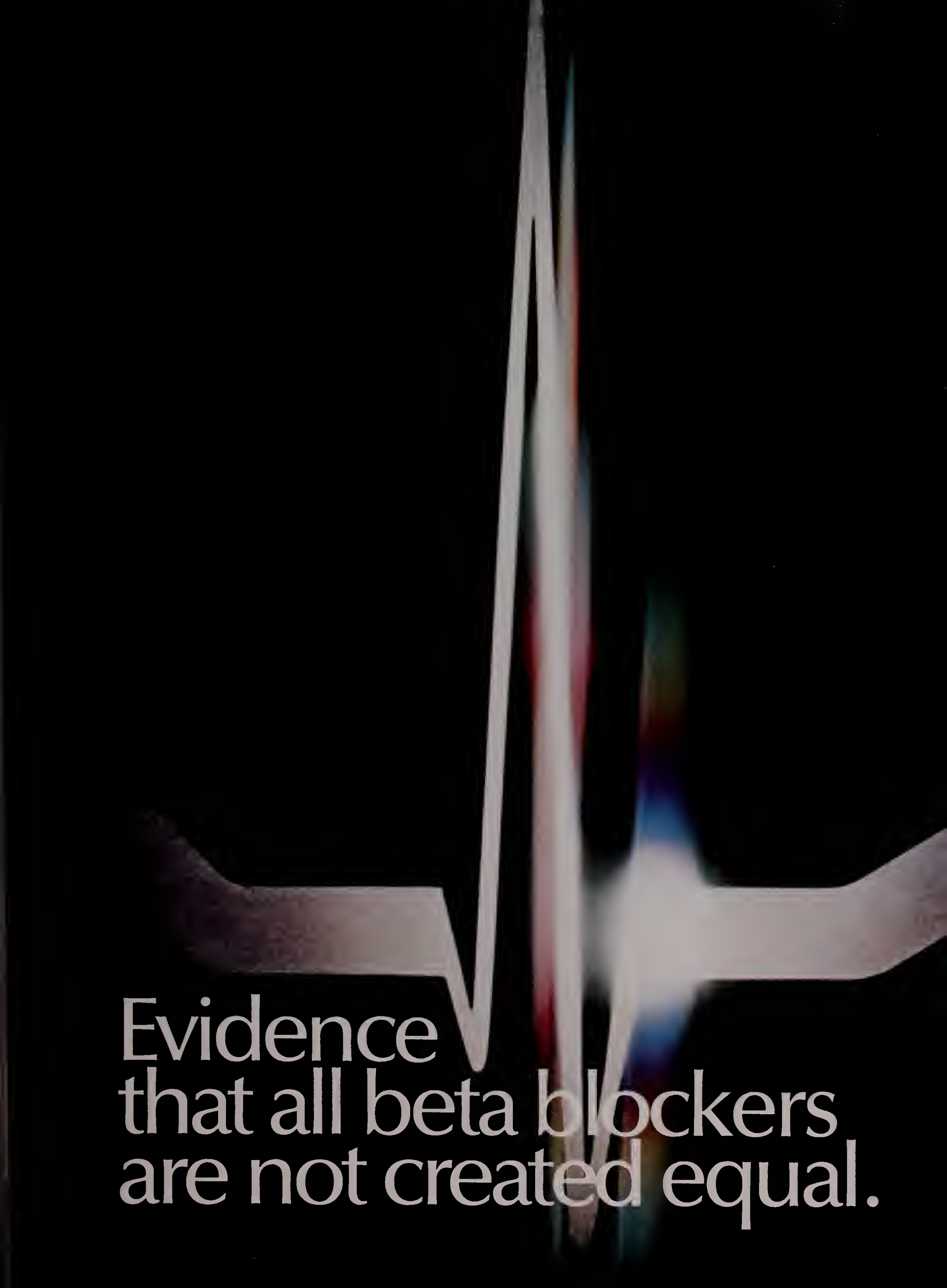

Evidence
that all beta blockers
are not created equal.

New studies uncover the potassium effects of beta-2 blockade

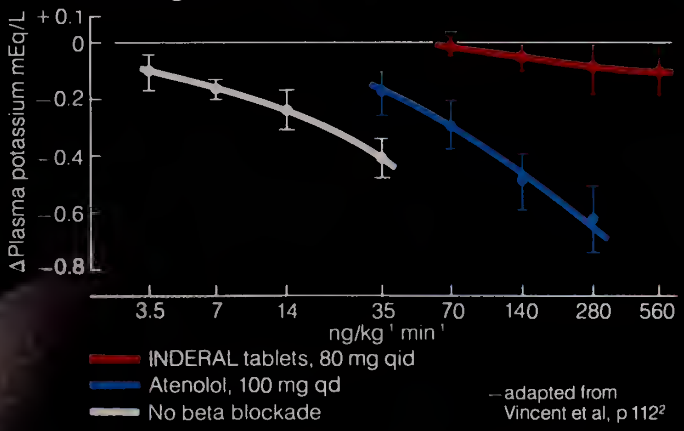
Clinical pharmacology data from the *New England Journal of Medicine:*

"...when normal young men are given infusions of epinephrine at levels such as those that circulate in patients with myocardial infarction, their serum potassium concentrations fall by about 0.8 mmol per liter. Hypokalemia is prevented by...beta-2 blockade."[1]

INDERAL (propranolol HCl) prevented beta-2 mediated hypokalemia

In a pharmacological study comparing INDERAL with atenolol, 10 hypertensive patients were infused with the nonselective beta agonist, isoproterenol, which also stimulates beta-2 mediated hypokalemia. At doses high enough to overcome beta-1 mediated heart rate reductions, the hypokalemia caused by isoproterenol was blunted by INDERAL, but not by atenolol.[2]

INDERAL compared with atenolol: change in plasma potassium after beta-agonist infusion[2]



—adapted from Vincent et al, p 112[2]

For beta-1/beta-2 blockade INDERAL (PROPRANOLOL HCl)

Please see last page for brief summary of prescribing information.

Epinephrine-induced hypokalemia can intensify diuretic-induced hypokalemia

From the *Lancet:*

"Although both diuretics and adrenaline are known to cause hypokalaemia, we believe that this is the first demonstration that these two factors can act in an additive manner. Routine monitoring of serum potassium in patients on thiazide diuretics may underestimate the risks of hypokalaemia."[3]

Epinephrine drives potassium into cells—an effect that has been shown to be under beta-2 receptor control[4]; thiazides promote excretion of potassium. When these actions occur together, hypokalemia can intensify significantly.[3]

Epinephrine-induced hypokalemia can cause ECG abnormalities typical of other forms of hypokalemia

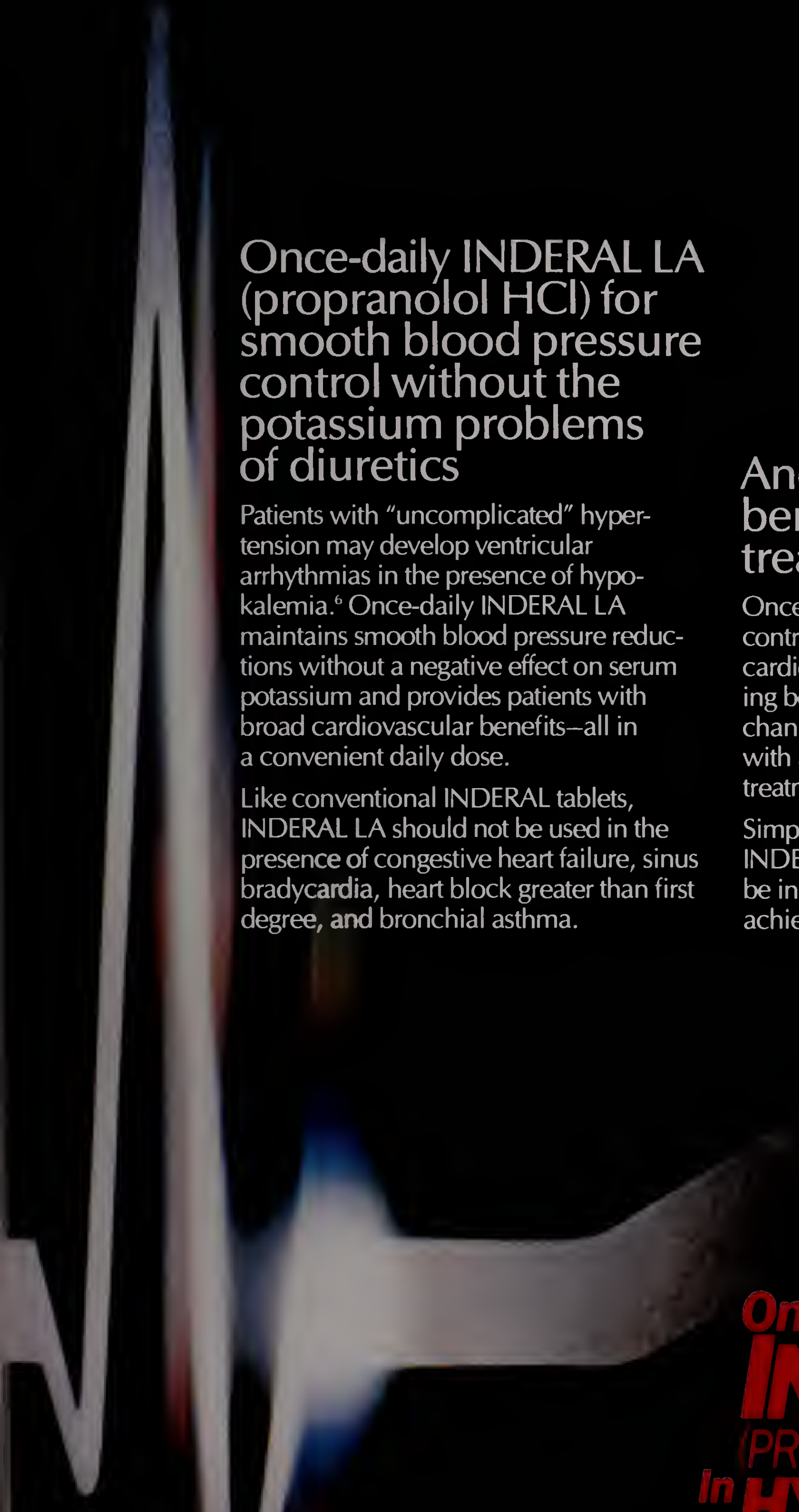
In a study of the effects of epinephrine-induced hypokalemia on the electrocardiogram, it was shown that levels of plasma epinephrine similar to those observed during myocardial infarction can produce changes in ventricular repolarization, which are reflected in T-wave flattening and QT prolongation in normal subjects.[5]

In clinical pharmacology studies of hypertensive and normal patients, epinephrine-induced hypokalemia was prevented by beta-2 blockade.[2,4]

For beta-1/beta-2 blockade INDERAL®
(PROPRANOLOL HCl) TABLETS

Please see last page for brief summary of prescribing information.

Right from the start
in hypertension…



Once-daily INDERAL LA (propranolol HCl) for smooth blood pressure control without the potassium problems of diuretics

Patients with "uncomplicated" hypertension may develop ventricular arrhythmias in the presence of hypokalemia.[6] Once-daily INDERAL LA maintains smooth blood pressure reductions without a negative effect on serum potassium and provides patients with broad cardiovascular benefits–all in a convenient daily dose.

Like conventional INDERAL tablets, INDERAL LA should not be used in the presence of congestive heart failure, sinus bradycardia, heart block greater than first degree, and bronchial asthma.

And for lifetime benefits in foundation treatment of angina

Once-daily INDERAL LA provides 24-hour control of angina symptoms–plus the cardiovascular benefits of the world's leading beta blocker. And unlike calcium channel blockers, INDERAL LA, alone or with a nitrate, is recommended for first-line treatment of stable angina.

Simply start new patients on 80 mg INDERAL LA once daily. Dosage may be increased to 160 mg once daily to achieve maximal control.

Once-daily
INDERAL LA
(PROPRANOLOL HCl)
In HYPERTENSION
and ANGINA

The appearance of these capsules is a registered trademark of Ayerst Laboratories
Please see last page for brief summary of prescribing information.

80 mg 120 mg 160 mg

INDERAL®

(PROPRANOLOL HCl) TABLETS

10 mg 20 mg 40 mg 60 mg 80 mg 90 mg

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Once-daily INDERAL® LA

(PROPRANOLOL HCl) LONG ACTING CAPSULES

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BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULARS.)*

INDERAL® (propranolol hydrochloride) **Tablets and Injectable**

INDERAL® LA (propranolol hydrochloride) **Long Acting Capsules**

INDICATIONS AND USAGE—INDERAL Tablets

Hypertension: INDERAL (propranolol hydrochloride) is indicated in the management of hypertension. It may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic INDERAL is not indicated in the management of hypertensive emergencies

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL is indicated for the long-term management of patients with angina pectoris.

Cardiac Arrhythmias:

1) Supraventricular arrhythmias

a) Paroxysmal atrial tachycardias, particularly those arrhythmias induced by catecholamines or digitalis or associated with the Wolff-Parkinson-White syndrome (See W-P-W under WARNINGS.) b) Persistent sinus tachycardia which is noncompensatory and impairs the well-being of the patient. c) Tachycardias and arrhythmias due to thyrotoxicosis when causing distress or increased hazard and when immediate effect is necessary as adjunctive, short term (2-4 weeks) therapy May be used with, but not in place of, specific therapy. (See Thyrotoxicosis under WARNINGS) d) Persistent atrial extrasystoles which impair the well-being of the patient and do not respond to conventional measures e) Atrial flutter and fibrillation when ventricular rate cannot be controlled by digitalis alone, or when digitalis is contraindicated

2) Ventricular tachycardias

Ventricular arrhythmias do not respond to propranolol as predictably as do the supraventricular arrhythmias. a)Ventricular tachycardias. With the exception of those induced by catecholamines or digitalis, INDERAL is not the drug of first choice In critical situations when cardioversion technics or other drugs are not indicated or are not effective, INDERAL may be considered If, after consideration of the risks involved, INDERAL is used, it should be given intravenously in low dosage and very slowly (See DOSAGE AND ADMINISTRATION) *Care in the administration of* INDERAL *with constant electrocardiographic monitoring is essential* as *the failing heart requires some sympathetic drive for maintenance of myocardial tone*. b) Persistent premature ventricular extrasystoles which do not respond to conventional measures and impair the well-being of the patient.

3) Tachyarrhythmias of digitalis intoxication

If digitalis-induced tachyarrhythmias persist following discontinuance of digitalis and correction of electrolyte abnormalities, they are usually reversible with *oral* INDERAL Severe bradycardia may occur (See OVERDOSAGE.) Intravenous propranolol hydrochloride is reserved for life-threatening arrhythmias Temporary maintenance with oral therapy may be indicated. (See DOSAGE AND ADMINISTRATION in the package circulars)

4) Resistant tachyarrhythmias due to excessive catecholamine action during anesthesia

Tachyarrhythmias due to excessive catecholamine action during anesthesia may sometimes arise because of release of endogenous catecholamines or administration of catecholamines When usual measures fail in such arrhythmias, INDERAL may be given intravenously to abolish them. All general inhalation anesthetics produce some degree of myocardial depression Therefore, when INDERAL (propranolol hydrochloride) is used to treat arrhythmias during anesthesia, it should be used with extreme caution and constant ECG and central venous pressure monitoring (See WARNINGS.)

Myocardial Infarction: INDERAL is indicated to reduce cardiovascular mortality in patients who have survived the acute phase of myocardial infarction and are clinically stable.

Migraine: INDERAL is indicated for the prophylaxis of common migraine headache The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use

Hypertrophic Subaortic Stenosis: INDERAL is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta receptor stimulation. Clinical improvement may be temporary

Pheochromocytoma: After primary treatment with an alpha-adrenergic blocking agent has been instituted, INDERAL may be useful as *adjunctive* therapy if the control of tachycardia becomes necessary before or during surgery

It is hazardous to use INDERAL unless alpha-adrenergic blocking drugs are already in use, since this would predispose to serious blood pressure elevation. Blocking only the peripheral dilator (beta) action of epinephrine leaves its constrictor (alpha) action unopposed

In the event of hemorrhage or shock, there is a disadvantage in having both beta and alpha blockade since the combination prevents the increase in heart rate and peripheral vasoconstriction needed to maintain blood pressure.

With inoperable or metastatic pheochromocytoma, INDERAL may be useful as an adjunct to the management of symptoms due to excessive beta receptor stimulation

INDICATIONS AND USAGE—INDERAL LA Long Acting Capsules

Hypertension: INDERAL LA (propranolol hydrochloride) is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

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CONTRAINDICATIONS. INDERAL and INDERAL LA are contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma; 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL

WARNINGS. CARDIAC FAILURE Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL (propranolol hydrochloride) therapy Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors

MAJOR SURGERY The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures

INDERAL, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e g , dobutamine or isoproterenol However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers

DIABETES AND HYPOGLYCEMIA Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes In these patients, it may be more difficult to adjust the dosage of insulin

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm Propranolol does not distort thyroid function tests

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker In one case this resulted after an initial dose of 5 mg propranolol

PRECAUTIONS. *General:* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

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NEW YORK STATE
JOURNAL OF MEDICINE

December 1984 • Volume 84, Number 12

COMMENTARIES

The addict's angioaccess

Complications of exotic vascular injection sites

The problems of angioaccess were discovered by abusers of drugs before the advent of hemodialysis, chemotherapy, and total parenteral nutrition. The addict's problems just begin once the external substance is introduced into the blood stream. Immediately after intravascular instillation, the user is subject to the vasoactive properties of the drugs, the occlusive phenomenon of the impact of the impurities mixed with the drug, and the possibility of circulatory disruption, fistula formation, or occlusion of the blood vessel chosen for the injection site. The local and systemic effects of the drug are the next problems for the addict. Narcosis often results in the addict's postural slump persisting in a stuporous condition for hours, thus crimping or compromising the circulation to extremities on which the body weight rests.

The next order of threats to life and limb comes from the local and systemic inoculum carried with the injected drug that can cause the septic complications of blood-borne infections. The infection is often self-sustaining from the local injection site, which might form a mycotic aneurysm, or from other sites in the circulatory system that can develop infections such as endocarditis, pulmonary abscesses, and valvulitis. The infecting agents travel through the body from the injection site to distant target organs, as has been reviewed.[1] Of the serious consequences of intravascular drug use (Fig 1), many relate directly to the site of injection and are complicated by the problem of angioaccess.

In this issue of the *Journal*, Pace, Doscher and Margolis[2] report on three patients who resorted to femoral injections after running out of other access sites, each with life- or limb-threatening complications—death in one instance and long-term disability in the remaining two who survived. The one fatality resulted from deep venous thrombosis and septic pulmonary emboli with migrating pulmonary abscesses. This clinical pattern is so characteristic of intravenous drug abuse that a radiologist may make the diagnosis by reviewing a series of chest films with this pattern of "mainliner's lung."[3] Two of the patients reported[2] had severe complications from femoral venous self-injection. One patient had a septic arteriovenous fistula which, though treated, led to end-stage endocarditis that destroyed both aortic and mitral valves. The other patient probably suffered a ruptured mycotic aneurysm in the superficial femoral

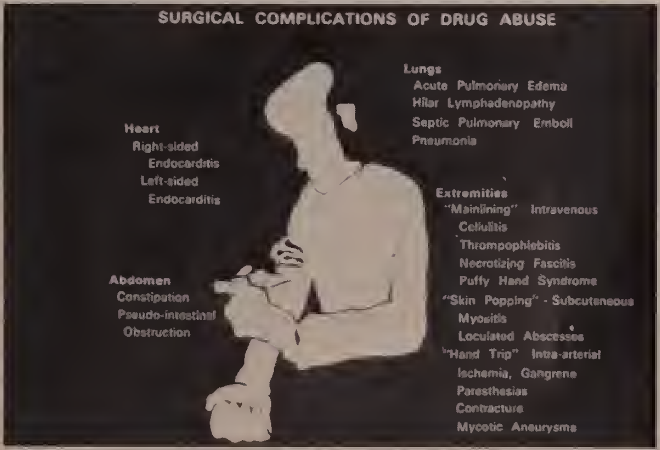

FIGURE 1. The complications of intravenous drug injection are compounded when the obliteration of superficial peripheral veins forces the use of deep venous and arterial injection sites.

artery which was recognized while the patient was in the hospital, but the necessary ligation, even though followed by extra-anatomic graft revascularization, resulted in a dysfunctional limb. One of the reasons that there might be justifiable pessimism about the "successful management" of angioaccess complications is the low rate of rehabilitation of the addict and the inevitable recontamination of the distorted vascular tree or its graft prosthesis.

The antecubital fossa on the side of the nondominant hand is the preferred site for self-administration of most intravenous drugs. This relatively "quick and clean" site for access to the cephalic and basilic venous systems becomes sclerotic early in the course of addiction, after repeated episodes of phlebitis. An addict must search for other superficial veins within the reach of the less dextrous hand after using up the preferred side. With the progressive loss of superficial venous access sites, the addict may turn to intra-arterial injection or, educated by street-wise suppliers or through experience gained while in the hospital, attempt deep venous access.

Intra-arterial injection[3] may be accidental, when the targeted deep vein is missed or penetrated, or it may be purposeful for reasons of special sensations the addict may seek. The artery offers access to the circulation when no useable veins remain; a palpable pulse serves as an indicator for a concomitant vein in the deep venous system. However, some addicts may try to achieve the special sensation known as a "flash" or "hand trip" that results from intra-arterial injection. Tingling and paresthesias result, and an additional sensation combines with the numbing effect of the drug in recirculation.

The use of deep venous access may be a result of "public education" by the medical profession, particularly in addicts who have frequent hospital stays. Addicts may be treated by or observe the use of special central venous access techniques, such as subclavian catheterization, internal jugular puncture, or femoral venous cannulation. Equipped with this knowledge, they may spread the use of these deep venous cannulation techniques to other addicts, with an open market for this information in the street.

The vascular lesion in the "flash" of intra-arterial injection has several causes. Intimal damage secondary to the drug may cause necrosis of the arterial wall and thrombus propagation in the arterial tree, even if the drug is not injected sub-intimally. Extreme vasoconstriction has been postulated with the release of vasoactive amines from the injured artery; platelet-activated vasoconstriction has also been reported.[4] Microembolization of the small vessels—plugged with the excipient particulate debris used as diluent for the narcotics—is likely with intra-arterial injection.[4] Direct arterial embolization and severe vasospasm can be seen with angiography of the affected extremity.

Various injectable drugs and excipients never intended to be injected give rise to vascular lesions by a number of mechanisms: these include vasospasm, norepinephrine release, intimal damage in thrombosis, platelet aggregation and hemolysis, acid crystal embolization, particulate microembolism of the excipients, idiosyncratic reactions, and necrotizing arteritis.[4]

The chronic addict, generally suffering from immunosuppression, usually injects a substance without assuring sterility, using only token antiseptic techniques. This is particularly true for agents that are solid or powder when purchased and that are rendered semiliquid by heating in a spoon over a candle before injection. Microbial contamination is then spread to the inflamed vessel, with lowered resistance to the injection; septicemia is the not so surprising result. At one time, the organism that was cultured would suggest the origin of the drug injected. For example, on the east coast of the United States, clostridial infection, and tetanus in particular, is a common complication; this finding is not frequently reported on the west coast. At the time this phenomenon was investigated, the course of the infection was thought to be the diluent with which the heroin was "cut" on the street. Heroin merchandisers on the east coast used quinine to cut the heroin, because quinine had a similar appearance and consistency, and mixed well with heroin in the melting spoon. But one of quinine's properties includes a high oxidation-reduction potential, and when injected with the drug it created appropriate conditions for anaerobic growth.

The report by Pace et al[2] proposes that the femoral triangle is a death trap for the addict, and that the use of exotic, deep venous injection sites or intra-arterial injections is an indication of an end-stage addict. These angioaccess complications generally reflect a long-term habit that exhausts the more manageable injection sites, and are sometimes indicative of desperation for the immediate gratification of an intravascular "hit." When coupled with nutritional deficits, immunosuppression, the trauma that results from inappropriate use of machinery and locomotion under the influence of drugs, and the blunt and penetrating wounds of violence frequently encountered in the criminal support of the addict's habits, the use of any of these deep vascular access sites carries with it a grave prognosis.

GLENN W. GEELHOED, MD
Associate Professor
Department of Surgery
George Washington University
Medical Center
2150 Pennsylvania Ave, NW
Washington, DC 20037

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Drug abuse prevention: the physician's responsibility

Two articles in this issue of the *Journal*[1,2] address novel complications of drug abuse. Such information not only adds to the body of medical knowledge but also is of obvious value in the expeditious diagnosis and management of similar patients. Somewhat distressing, however, is the consensus that such complications are expected to increase as the recreational and non-medical use of drugs proliferates. This underscores a sense of frustration in the treatment of drug abuse and its complications. For one, the surgeon or internist may expect to see the addict or aficionado of recreational drugs at some future time with additional complications. The hospital experience will do little, if anything, to curtail the usage of drugs or alter the lifestyle of the majority of these individuals.

A second area of frustration lies in the realization that at least some individuals who are not yet experimenting with drugs will eventually become drug abusers and addicts, perhaps to grace the medical literature as future case reports or statistical compilations. Preventing the evolution of this population into the realm of recreational drug abuse is an issue that should concern all physicians regardless of specialty. Indeed, the far-reaching social, economic, and medical impact of drug abuse should mandate involvement by medical practitioners collectively and individually.

The orientation of our society toward drugs has been influenced by the news media, the entertainment industry, the medical profession, and the pharmaceutical industry.[3] The result is a widespread proliferation of the recreational and non-medical use of drugs in unprecedented proportions. To alter the attitude that has been adopted toward drugs, and thereby curtail the consequences of drug abuse, it is necessary to affect the balance of supply and demand. For illicit drugs, law enforcement agencies can have limited success in curtailing their availability on the streets. For prescription drugs, the clinician must limit the supply through appropriate prescribing practices, and by being aware that persons who abuse drugs are experts in duping unwary physicians into supplying them with the drug of their choice.[4]

Prevention of drug abuse, however, must focus on educating those not yet involved with drugs but who will assuredly become exposed to them at a future time. While this group includes many adults, the majority are adolescents. This latter group, in my experience, has a genuine desire to obtain factual information about drugs, which the physician is in a unique position to provide. However, a physician must be aware of what drugs are prevalent in the community and how they are used. Newsstand periodicals oriented toward adolescents and the drug culture can divulge a wealth of such information, while drug treatment centers and medical examiners' offices can provide an index of the drugs that are prevalent in a given locale. In south Florida, for example, medical examiners have witnessed an alarming increase in cocaine-induced fatalities within the past year, and, more recently, the reappearance of deaths due to heroin overdoses. Such data forecast a changing drug profile in the community which will eventually be manifest in hospital admissions and drug treatment programs.

For the betterment of patient care it is important that physicians educate each other about the complications of drug abuse. Of equal importance is that physicians assume a leadership role in translating this information into lay terms and disseminating it to those who are or will be exposed to recreational drug abuse. This can be accomplished in the physician's office by direct patient contact and by the dissemination of literature selected by the physician. Also, active interaction with a variety of civic and school organizations is of immense value in providing an awareness of drug abuse and its potential hazards. Only by educating ourselves and the potential victims of drug abuse can we hope to curtail the non-medical use of drugs and, by inference, prevent the complications of drug abuse.

CHARLES V. WETLI, MD
Deputy Chief Medical Examiner
Medical Examiner Department
1050 NW 19th St.
Miami, FL 33136

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Radiation-induced breast cancer

It has been well established through animal experiments and epidemiologic studies of humans that relatively high doses of ionizing radiation can induce breast cancer in women.[1,2] In fact, the female breast is believed to be one of the most susceptible organs to radiation-induced carcinogenesis. Evidence for this association is based on long-term follow-up studies of irradiated populations, most notably the atomic bomb survivors in Japan,[3] women receiving therapeutic radiation for benign breast conditions,[4,5] and women exposed to multiple chest fluoroscopies during the course of pneumothorax treatment for tuberculosis.[6-8] Collectively, these studies continue to enhance our understanding of the carcinogenic effects of ionizing radiation.

Pathologic studies indicate that radiation-induced breast cancers cannot be distinguished morphologically from other breast cancers.[9,10] Therefore, evidence for an association is based on an observed dose-related excess of breast cancer in irradiated female populations.[2] While many functional forms of a dose-response relationship have been examined, a simple linear model is consistent with the pattern of risk in most studies.[11] Although more complex, non-linear models cannot be ruled out, relationships that deviate greatly from linearity do not adequately describe the existing data. It is of interest that highly fractionated radiation has about the same potential for inducing breast cancer as does unfractionated radiation. Similar estimates of excess risk among populations with markedly different patterns of exposure, such as the atom bomb survivors (single dose), patients with postpartum mastitis (several closely spaced exposures), and patients with tuberculosis (multiple widely spaced exposures) support this conclusion.[11]

The effects of radiation in terms of increasing a woman's risk for breast cancer appear to be long lasting. Following a minimum latent period of about 10 years, women who have been exposed to radiation continue to have greater than expected rates of breast cancer for at least 30 to 35 years after the time of irradiation.[4,6] Lifetime follow-up studies of existing cohorts will be required to determine whether this effect is permanent. However, the temporal pattern of risk is seemingly unaltered by exposure to ionizing radiation. In other words, while women who were exposed to radiation have higher rates of breast cancer than do women of a similar age who were not exposed, the shape of their respective age-specific incidence curves is similar.

Age at exposure is a major factor in radiation-induced carcinogenesis. Until recently, it appeared that irradiation during the second decade of life, especially around the time of menarche, conferred the greatest risk of breast cancer.[3,11] Furthermore, follow-up studies of the atom bomb survivors provided little evidence of radiation-induced breast cancer among women who were less than 10 years of age at the time of exposure.[3] These observations gave rise to the theory that the female breast is most susceptible to the carcinogenic effects of radiation during periods of rapid breast development when mitotic activity is high, while the immature prepubescent gland may be relatively unaffected by exposure to ionizing radiation.[12]

Recent findings make this theory less tenable. Based on the latest follow-up survey of the atom bomb survivors, an increased risk of breast cancer is now apparent among the women who were nine years of age or younger when exposed; moreover, the relative risk estimate for radiation-induced breast cancer is highest among this group and progressively decreases with increasing age at exposure.[13] An excess of breast cancer has also been found among women who were irradiated in infancy for an enlarged thymus gland.[14] In both studies, nearly a 35-year latent period elapsed before the radiation-induced breast cancers appeared. This suggests that the carcinogenic effect of radiation may not become apparent until one attains the age at which the natural incidence of breast cancer begins to rise. Certainly this is consistent with previous observations that radiation influences the magnitude of excess risk but not the temporal pattern of occurrence.

These findings, if verified in future follow-up studies, cast a new light on previous theories of radiation-induced carcinogenesis. Most importantly, the idea that the immature breast is insensitive to the carcinogenic stimuli of ionizing radiation is no longer valid. What these data suggest is that irradiation of the breast, whether it be in childhood or adulthood, alters the cells in such a way as to make them more susceptible to the tumor-promoting effects of other hormonally-mediated risk factors for breast cancer. Furthermore, since initiation of this process at an early age would maximize the period of time for tumor promotion, one might expect the risk of radiation-induced breast cancer to be highest among those exposed early in life. This is consistent with the recent findings in the atom bomb study.[13] This theory would also be consistent with the observation that radiation-induced breast cancer is very rare among males, since even if initiation has occurred, men generally lack the requisite factors for tumor promotion.

Our knowledge of radiation-induced breast cancer, although fairly extensive, is by no means complete. The effect of low-dose exposure to radiation is a particular area of concern, especially in regard to the risk versus benefit of mammographic screening of asymptomatic women. As demonstrated by Land,[15] prohibitively large sample sizes would be needed in order to obtain direct estimates of risk by studying populations exposed to low levels of radiation. Therefore, we must rely on extrapolation from higher doses. Assuming a linear dose-response relationship, it is estimated that the absolute risk of radiation-induced breast cancer among American women exposed after the age of 20 years is 6.6 ± 1.9 excess breast cancers per 10^6 women per year per rad; based on a multiplicative model, there is an 0.42% ± 0.15% increase in the relative risk per rad.[16] Regarding the potential hazards of mammography, this suggests that a 35-year-old woman exposed to one rad of radiation would increase her lifetime risk of spontaneous breast cancer from 7.58% to 7.61%. This seemingly small impact takes on more significance when applied to a large population—if one million women were each exposed to one rad of radiation, approximately 234 to 425 excess breast cancers would be expected to occur during their lifetime.[17] Although some controversy may still exist concerning the routine use of mammography for screening asymptomatic women who are under the age of 50 years, a randomized controlled study has demonstrated that the benefits outweigh the risks among women over the age of 50 years.[18]

In addition to low dose exposure, other issues that require further investigation include the effects of irradiation in childhood and the interaction of ionizing radiation with other risk factors for breast cancer. Ongoing follow-up studies of irradiated populations offer the potential for enhancing our understanding of these important issues.

NANCY G. HILDRETH, PhD
Assistant Professor
Department of Preventive, Family,
and Rehabilitation Medicine
The University of Rochester
Medical Center
601 Elmwood Ave
Rochester, NY 14642

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Blood glucose monitoring at home

As evidence mounted that normoglycemia should be the treatment goal for patients with diabetes mellitus, the challenge was to find the tools and techniques to achieve and maintain blood glucose levels in the normal range (70 to 120 mg/dL). The first demonstration that normoglycemia was beneficial occurred in pregnant women with diabetes mellitus. Normalization of blood glucose levels in pregnant women with diabetes resulted in a dramatic reduction in infant mortality rates. The beneficial effects of normoglycemia then became evident in non-pregnant patients. There is preliminary evidence that disorders associated with diabetes mellitus, including nephropathy, neuropathy, retinopathy, and cardiovascular disease show delayed progression and, in some cases, regression when normoglycemia is sustained. This review on home blood glucose monitoring points out how this technology offers independence to the patient with diabetes.

The development of accurate and convenient methods of monitoring blood glucose levels at home has changed dramatically the style and goals of managing the disorder and the nature of the physician-patient relationship. As self-care becomes more practical, the transfer of responsibility for decision-making to the patient increases. Historically, this transition in roles was initiated in 1971 by a patient, Richard Bernstein, who adapted the Ames Eyetone Reflectance meter, designed for use in the physician's office, to use at home as part of a program of blood glucose control. This revolution triggered a rash of feasibility studies, beginning in 1978, which showed that blood glucose monitoring at home was manageable by patients of varied ages and backgrounds, and that it led to improved glucose control. In response, more sophisticated reflectance meters were introduced and were studied for accuracy and patient acceptance. By 1980, the patient was responsible for gathering information, while the physician remained in charge of insulin adjustments.

The introduction of blood glucose monitoring in the home led to improvements in the level of glucose control. For example, the information collected demonstrated the inadequacy of traditional insulin delivery systems and led to experimentation with the timing and number of injections. Another management strategy change was more subtle: finer adjustments in the timing and dosage of insulin were made possible by the knowledge of how a patient's daily life style affected blood glucose levels.

This information resulted in behavior changes by the patient as well as the physician. No longer did the patient have to take the advice of the medical specialist on faith; he or she could now observe the effects of behavior on blood sugar and begin to appreciate and manipulate the variables involved. The patient's increased understanding had a direct effect on compliance—blood sugar levels could often be controlled without changing the insulin regimens. This decision-making role was the second major step in the transfer of control to the patient. Patients can be gradually brought to the stage where they master the paradigms of insulin adjustment. This involves considerable investment of time and energy by the physician, nurse, and dietitian.

Allied health professionals may be involved in the decision-making process at all levels, from teaching technical skills to adjusting insulin dose and diet. It should be recognized that although insulin dose adjustment may be well within a patient's capability, that level of decision-making may not lie within the scope of responsibilities of allied health workers. The nurse and dietitian should be protected through a clear definition of roles and written protocols of what constitutes standard care. The legal questions surrounding the delegation of responsibility by the physician are as yet unresolved.

A second issue that should be addressed is that of the patient's response in the event that, despite careful attention to control, adverse health effects are still enountered. The reality is that in spite of one's best intentions and good behavior the future is not guaranteed, and complications occur. The extent to which good control affects the development and progression of the complications of diabetes is being studied. Patients' strategies to cope with diabetes may include unrealistic expectations. Physicians should be cautious that their enthusiasm for a promising new technique does not generate unrealistic hopes. Rather, they should present these programs as the best available alternative to help patients with a serious chronic disease.

The ultimate in health care delivery would be to minimize the role of the physician by programming a computer not only to scan the blood glucose data but also to derive optimal insulin delivery plans. This technology is being pursued. Thus, in the not too distant future, each person with diabetes could depend on a pocket computer for determining insulin dose. The impact of this development on the doctor-patient relationship would vary according to the needs of each patient.

Home blood glucose monitoring has emerged as a powerful tool whereby persons with diabetes have gained independence and achieved better health care plans tailored to their needs.

ANNE DUCKLES, RN
LOIS JOVANOVIC, MD
The New York Hospital-
Cornell University Medical College
515 East 71st St.
New York, NY 10021

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LETTERS TO THE EDITOR

Address correspondence to Editor, New York State Journal of Medicine, *420 Lakeville Road, Lake Success, NY 11042. Letters should be typed double-spaced and include the signature, academic degree, professional affiliation, and address of each author. Preference is given to letters not exceeding 450 words, and every effort will be made to assure prompt publication. All letters are personally acknowledged by the Editor.*

Licorice induced hypokalemia

TO THE EDITOR: In the report of a case of paraparesis due to licorice induced hypokalemia (*NY State J Med* 84:296), the patient described is very much like one I wrote about in 1969 (*JAMA* 208:1909). The most dramatic feature was the hypokalemic myopathy, which cleared soon after stopping licorice and giving potassium by mouth.

That such a severe disease can be due to the ingestion of licorice is not well known either to doctors or patients.

I agree with the final statement of the authors that patients with hypertension and those receiving diuretic therapy should be warned of the potential hazard of excessive licorice ingestion. I believe that licorice candy is a potent drug and should be withdrawn from the market.

LOUIS PELNER, MD
161 Rugby Rd
Brooklyn, NY 11226

This letter was sent to the licorice division of Y&S Candies, Hershey Foods Corp, which chose to make no formal comment on the letter at this time.

—Editor

Benign infiltrative lipomatous lesions

TO THE EDITOR: The infiltrating lipoma is a benign tumor but frequently causes concern to both clinicians and pathologists due to its large size, deep location, and infiltrative growth patterns.[1-5] Two cases of this entity prompted this report, with a brief comment on the clinicopathologic features.

Case Reports. The first patient, a 39-year-old man, was admitted for treatment of a large axillary mass that had increased in size during the previous five years. Total excision of the mass was performed; the surgical specimen consisted of two irregular masses of adipose tissue measuring 25 × 20 × 7 cm and weighing 1,150 g. No definite capsule was discernible; white and brown firm areas were visible amid the fat. The second patient was a 4-year-old boy with a soft tissue mass over the right maxillary area since birth; the mass had gradually attained the present size of 4 cm. The clinical diagnosis was a hemangioma, and the child was followed in the clinic until the present admission for elective surgery. At surgery, the mass was noted to be diffuse and poorly defined; the lower portion showed fibromuscular and fatty areas, and the upper portion involved multiple branches of the facial nerve. Due to the strategic location, only a partial excision could be carried out. On microscopic examination both masses showed infiltration of mature adipose tissue between the skeletal muscle fibers (Fig 1). Ischemic atrophy and fibrosis were observed in the focal areas.

Discussion. The two patients illustrate the diagnostic and therapeutic difficulties encountered in the management of infiltrating lipomas. In patient 1 the tumor margins were poorly delineated, whereas in patient 2 the infiltrative nature and strategic location of the mass precluded the possibility of a complete excision. These lesions have been reviewed by Dionne and Seemayer[1] and Kindblom et al.[2] In contrast to subcutaneous lipomas, which are more frequent in women, infiltrating lipomas are more common in men and occur between 30 and 60 years of age.[2] The shoulder and the thigh are the most common sites.[2] Two patterns of involvement are described: the intermuscular and the intramuscular forms. The former probably has its origin in the fascial septa and grows between muscle bundles with secondary infiltration of the fibers, whereas the latter occurs primarily within the muscle.[2,4,5]

Clinical symptoms are variable, depending on the size and location of the tumor. A characteristic feature is the change in the consistency and form of the mass, which becomes firm with contraction of the muscle.[1,2,5] On radiographic study the tumor is often clearly visible because of radiolucence,[2,5] while streaks of higher density material due to the muscle bundles may be seen.[2] The differential diagnostic considerations would include other soft tissue tumors, muscle herniation, muscle rupture, hematomas, parasitic cysts, and metastatic tumors.[2] Lipomas are uncommon[4,6] in the oral cavity; infiltrative lipomas of the head and neck in particular are unusual.[5] In such cases the preoperative diagnosis is again uncertain and lipomas may be mistaken for cysts, abscesses, or other benign tumors.[6]

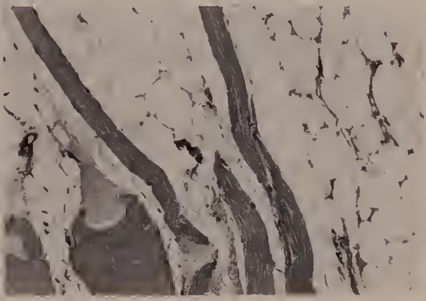

FIGURE 1. Photomicrograph showing mature adipocytes infiltrating skeletal muscle fibers. (Case 1, hematoxylin & eosin stain, original magnification × 250)

On gross examination the tumors were poorly defined, ranging in size from 2.5 to 18 cm.[5] Extensive infiltration of the skeletal muscle fibers by mature adipocytes was noted.[1-5] Secondary changes resulting from focal ischemia include atrophy and interstititial fibrosis.[2,5] The lack of cellular areas, atypical nuclei, number of mitoses, anaplasia, lipoblastic proliferation, myxoid changes, and stellate cells help to differentiate this lesion from a liposarcoma, but careful sampling of the tumor is mandatory.[1,2] The extensive literature on soft tissue liposarcomas contrasts sharply with the sparse reports on infiltrating lipomas, suggesting overinterpretation of these lesions as malignant.[1]

These tumors are characterized by slow growth—the average duration between the onset of symptoms and excision being six years.[1] With complete excision, the prospects of cure are excellent,[2,5] as evident in the study of Kindblom et al[2] where no recurrence or metastasis was noted in a follow-up of 33 cases. Successful therapy depends on recognition at the time of surgery that muscle infiltration has occurred and requires wide local excision, in addition to a frozen section to determine the extent of removal.

VENKITA JAGADHA, MD
GITA RAMASWAMY, MD
Department of Pathology
New York Medical College
Metropolitan Hospital Center
1901 First Avenue
New York, NY 10029

1. Dionne GP, Seemayer TA: Infiltrating lipomas and angiolipomas revisited. *Cancer* 1974; 33:732-738.
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Offshore medical schools

TO THE EDITOR: I am responding to the July 1984 issue of the *New York State Journal of Medicine* on offshore medical schools. I would like to address my comments to foreign medical graduates in general and, particularly, to the editorial "Commercialism in medicine," which I greatly enjoyed. My remarks are of a personal nature, but may have some general application as well.

Counting myself among foreign medical graduates (Basel, Switzerland-1939), I want to point out some fundamental differences between the refugee physicians who came here from Central Europe in 1938 to 1940, fleeing from Hitler's persecution, and the foreign doctors who have recently arrived. We were and are the lucky ones who made it to America, and we are forever grateful for the opportunities offered here. We had to have an "Affidavit of Support" from an American sponsor, preferably a relative, stating that we would not be a burden to the country for at least five years—the time it took to become a citizen. There was also the all-important quota number at the American consulates abroad, without which even the affidavit was worthless. Each European country had a number of immigration quotas, which were soon filled, and then one had to wait for another year.

I would like to honor my sponsor, a prominent physician and Quaker from Providence, RI, Dr Alexander M. Burgess, who literally saved my life without knowing me. He gave me his Affidavit on the recommendation of his son, Dr A. Burgess, Jr—a post-graduate student at Vienna in 1938, who befriended me. (Dr Burgess Sr later saved several other physicians from Vienna.)

We had to pass a language examination before we even could apply for state or national boards. Coming from a European background and tradition, these physicians were perhaps less commercialized and, by and large, tried to repay this country their great debt of gratitude by giving the best service they were capable of.

The next great wave of immigrant doctors came largely from the Far East. They often came as post-graduate students and stayed to fill the open residency positions in American hospitals.

The third group concerns American students, usually white and upper middle class, who could not get into medical schools in this country and went abroad to study. Many graduated from Italian and Belgian schools, which have good reputations, and then took their hospital training in the United States. They are apparently performing excellent service and cannot be distinguished from graduates of American schools on the basis of their positions in communities and hospitals across the country.

I think that some graduates of the offshore medical schools will eventually fall into this category once they have trained for two years in American medical schools and have completed the necessary residencies and post-graduate studies in this country.

HANS POLLAK, MD
82 Oakland Ave
Gloversville, NY 12078

Health care in Nicaragua

TO THE EDITOR: I should like to express my appreciation for the article by E. M. Petrack on health care in Nicaragua (*NY State J Med* 1984; 84:523-525). The subtitle promises "a social and historical perspective," and the paper does present a thoughtful and informative account not only of the observable facts, but of the larger context in which health care in Nicaragua (and in any country) must be viewed.

The medico-scientific function of the *New York State Journal of Medicine* is salutarily extended, I believe, when your readers' attention is directed to such relevant socio-political considerations. In the case of Nicaragua, the United States' role in halting, and even reversing, the hard won improvements in health for the people of a young and poor, but sovereign, nieghbor nation is a subject highly pertinent to our professional and civic concerns.

I. H. MAUSS, MD
Attending Pediatrician
North Shore University Hospital
300 Community Dr
Manhasset, NY 11030

Hazards of break dancing

TO THE EDITOR: Dr Copperman points out in the September issue of the *Journal* (1984; 84:422) that break dancing may lead to alopecia. Recently, I have come across a champion in break dancing who suffered from cervical cord injury as a result of the dancing. Other kinds of injuries that may result from break dancing include muscular strains, tendinitis, stress fractures, spondylolysis,[1] dislocations of the elbow, and ankle capsulitis.

Break dancing is very popular nowadays, especially among teenagers. As prevention is better than cure, public education regarding its potential hazards is of utmost importance.

ALEXANDER K. C. LEUNG, MD
Clinical Assistant Professor
Department of Pediatrics
University of Calgary
Alberta Children's Hospital
1820 Richmond Rd SW
Alberta, Canada T2T 5C7

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Uremic hypoglycemia

A preventable life-threatening complication

M. M. AVRAM, MD, ROBERT E. WOLF, MD, AMADO GAN, MD, ABE N. PAHILAN, MD,
SUNG KU PAIK, MD, MICHAEL IANCU, MD

ABSTRACT. Spontaneous hypoglycemia is often recognized as a uremic complication. Its pathogenesis remains poorly understood, although many factors including malnutrition, hepatic insufficiency, medications, and septicemia have been implicated. We report on six nondiabetic patients with uremia receiving maintenance dialysis in whom this complication developed. There were three men and three women, ranging in age from 25 to 91 years of age (mean age, 48.6 years). Hypoglycemia was documented in all patients, with serum glucose levels less than 25 mg/dL in all patients and less than 4 mg/dL in two patients. Five of six patients had serum albumin levels below normal, and all had endogenous creatinine clearance of 5 mL/min or less. Four patients received propranolol on the day of a hypoglycemic episode.

We infer that the most prevalent pathogenetic sequence in these patients appears to be liver dysfunction related to persistent uremia, in addition to superimposed hepatic stress which, in this series, was provoked by propranolol in four patients.

(NY State J Med 1984; 84:593–596)

INTRODUCTION

Uremia induces abnormal carbohydrate metabolism, manifested most often by hyperglycemia on fasting and a hyperglycemic response to oral or intravenous glucose.[1] At the other extreme of glucose regulation, reports document the occurrence of spontaneous hypoglycemia in diabetic[2–4] and nondiabetic[5–9] uremic patients. The pathogenesis of paroxysmal hypoglycemia during the course of renal insufficiency has not been established. Hypoglycemia has been associated with malnutrition,[2–4,9] substrate deficiency,[10] septicemia,[11,12] hepatic cirrhosis,[12] drug toxicity,[13–16] and aspirin[17] and disopyramide ingestion.[18,19]

To assess the prevalence of spontaneous hypoglycemia in patients with renal insufficiency, we reviewed records of 210 patients seen during the past two years and found six cases (2.9% incidence).

PATIENTS AND METHODS

We reviewed the records of 210 patients with uremia seen in consultation, and patients undergoing chronic dialysis, from January 1980 through December 1981 to identify episodes in which a blood glucose concentration of 25 mg/dL or less was recorded. Patients with insulin-dependent diabetes were excluded from the survey.

Blood glucose measurements were performed by a glucose oxidase method, using an autoanalyzer (Technicon). Insulin levels were determined by radioimmunoassay (Pharmacia, Sweden), and hydrocortisone levels were determined by competitive protein-binding radioassay (Schwart/Mann). Other laboratory tests were performed in the main hospital laboratory, according to standard techniques.

Case 1. Uremia due to nephrosclerosis developed in a 91-year-old man. In 1972 he was found to have marked cardiomegaly, aortic insufficiency, and hepatomegaly. There was no history of hypertension or diabetes mellitus. In 1976 he was hospitalized for congestive heart failure, at which time his bood urea nitrogen level was 61 mg/dL, and his serum creatinine level was 4.2 mg/dL. His blood glucose was 113 mg/dL. In 1979 uremia developed; blood urea nitrogen level was 103 mg/dL and serum creatinine level was 10.4 mg/dL. He began intermittent peritoneal dialysis using 48, 2-liter exchanges each week; this was continued for about one year. In 1980 he was admitted to the hospital with fever and abdominal pain. Physical examination revealed a thin man. Lateral displacement of the point of maximum intensity was thought to be due to an enlarged heart. The lungs were clear to auscultation. An enlarged liver was noted on palpation and percussion; rebound tenderness indicated peritonitis. The blood glucose level was 135 mg/dL, and the total serum protein level was 5.0 g/dL, with a serum albumin level of 2.4 g/dL. *Staphylococcus epidermidis* grew on cultures from the peritoneal fluid from three separate collections. Treatment for peritonitis was started.

Three days after admission the patient was stuporous and responded promptly to intravenous injection of hypertonic glucose. The blood glucose concentration before glucose administration was 18 mg/dL. During the next day he suffered 10 additional episodes of hypoglycemia, with blood glucose levels ranging from 21 to 48 mg/dL. Insulin levels on four different occasions and a fasting hydrocortisone level were within normal limits. Serum growth hormone level was 1.6 mg/dL (normal, 0 to 5 mg/dL) when the blood glucose level was 28 mg/dL. The patient died on the fifth hospital day. Permission for autopsy was refused, but the immediate cause of death was thought to be related to hypoglycemia.

Case 2. A 78-year old man had renal failure due to obstructive uropathy. He was treated with intermittent peritoneal dialysis, using 48 runs of 1.5% Dianeal solution weekly. There was no history of diabetes mellitus.

Six months later he came to the emergency room with seizures that responded to intravenous hypertonic glucose administra-

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From the Department of Medicine, Division of Nephrology, Avram Center for Kidney Diseases, The Long Island College Hospital, 340 Henry St, Brooklyn.
Address correspondence to Dr Avram, Chief, Division of Nephrology, The Long Island College Hospital, 340 Henry St, Brooklyn, NY 11201.

tion. The blood glucose level prior to administration of glucose was 21 mg/dL. All episodes occurred before the start of peritoneal dialysis. A chest film showed pneumonia in the lower lobe of the right lung. Laboratory test determinations included a total protein level of 4.2 g/dL, and a serum albumin level of 1.9 g/dL. Serum enzyme measurements showed a creatinine phosphokinase value of 1,595 U/L (normal, 1 to 225 U/L) and a lactic dehydrogenase level of 295 U/L (normal, 50 to 250 U/L). The pneumonia responded to penicillin. Plasma cortisol response rose from a baseline of 10 mg/dL (normal, 5 to 25 mg/dL) to 34 mg/dL eight hours after adrenocorticotropic hormone stimulation. Hypopituitarism was excluded by a serum thyroxine level of 6.2 mg/dL (normal, 5.5 to 11.5 mg/dL), and a triiodothyronine uptake of 34.6% (normal, 24 to 36% uptake). The thyroid stimulating hormone level was 4.6 Mcu/dL (normal, 1.0 to 8.0 Mcu/dL), prolactin value was 57 U (normal, 2 to 15 U), and growth hormone level was 26.1 ng/mL (normal, 0 to 5.0 ng/mL). The elevated prolactin and growth hormone values were consistent with chronic uremia.[20] When the patient was discharged from the hospital, his blood glucose level was within normal limits. There were no other recorded hypoglycemic episodes. He died months later because of combined cardiac and pulmonary failure.

Case 3. A 25-year old man became uremic due to chronic glomerulonephritis. He was treated with maintenance hemodialysis three times a week. The dialysate glucose concentration was 200 mg/dL. Hypertension was treated with hydralazine, prazosin, and propranolol. During the third month of dialysis therapy, abdominal pains, headache, and lethargy developed. His blood pressure was 230/140 mm Hg. The blood glucose level on admission was 13 mg/dL.

The patient responded promptly to treatment with intravenous glucose. His blood urea nitrogen level was 104 mg/dL, and the serum creatinine level was 22 mg/dL. Serum electrolyte and enzyme values were within the normal range. All medications except hydralazine were discontinued. There have been no further episodes of hypoglycemia.

Case 4. A 34-year-old woman had renal failure due to malignant hypertension, noted at the 30th week of gestation. Her blood pressure then was 250/120 mm Hg, and she had 2+ proteinuria and 2+ pitting pretibial edema. Her blood urea nitrogen level was 70 mg/dL, and the serum creatinine value was 3.4 mg/dL. Her blood pressure was controlled with hydralazine. She went into premature labor and delivered a stillborn baby at 31 weeks. She was unavailable for follow-up study until eight months later, when she had severe headaches and diplopia, nausea, vomiting, and lethargy. Her blood pressure was 270/140 mm Hg, her blood urea nitrogen level was 180 mg/dL, and her serum creatinine value was 16 mg/dL. Hemodialysis was instituted, and her symptoms improved. Antihypertensive medications included propranolol and clonidine. During her sixth month of dialysis, the patient came to the emergency room in a stuporous state. She responded promptly to 75 g of intravenous glucose therapy. A blood glucose level determined before glucose administration was 3 mg/dL. She has maintained a stable weight during the last 16 months. A serum electrolyte study showed that her serum potassium level was 6.8 mEq/L. There was a severe anion gap metabolic acidosis. Her serum bicarbonate value was 9 mEq/L, and her arterial blood pH was 7.18. Serum lactate levels were not obtained. Metabolic acidosis was corrected with intravenous sodium bicarbonate therapy. No focus of infection was discovered. No recurrence of hypoglycemia has occurred. Her blood pressure is currently controlled with clonidine and prazosin.

Case 5. A 35-year old woman began receiving maintenance hemodialysis in 1974 because of uremia due to chronic glomerulonephritis. She did not adhere to dietary salt limitations and suffered excessive weight gain and severe hypertension between dialysis sessions; she also missed scheduled hemodialysis treatments. Because of failure to achieve control of phosphate levels—due to dietary indiscretion and refusal to take prescribed aluminum hydroxide antacids—severe renal osteodystrophy developed. Her serum parathyroid hormone levels were about 2,000 pgEq/mL (normal, 167 to 323 pgEq/mL). She refused a subtotal parathyroidectomy.

The patient's antihypertensive regimen consisted of hydralazine and propranolol, which she did not take. When her medications were given immediately after each hemodialysis, better blood pressure control was achieved, but poor weight control persisted.

Three months after beginning the program of post-dialysis medication administration, she was brought to the emergency room in a comatose state. Her blood chemistry study results on admission included a serum potassium value of 8.7 mEq/L and a blood glucose level of 1 mg/dL. The electrocardiogram showed ventricular flutter followed by asystole. Attempts to effect cardiopulmonary resuscitation were unsuccessful, and the patient died.

Case 6. A 34-year old woman with uremia due to chronic glomerulonephritis had received maintenance hemodialysis since 1980. She did not adhere to the medical regimen and experienced excessive weight gain, abnormal electrolyte levels, and severe hypertension. She frequently missed scheduled hemodialyses. On one occasion she was admitted with hypotension, a serum potassium level of 9.6 mEq/L, and an electrocardiogram that showed ventricular fibrillation. These abnormalities reverted to normal with hemodialysis and intravenous glucose and insulin therapy. Hypertension was treated with hydralazine, propranolol, and prazosin.

Six months after initiation of maintenance hemodialysis she was admitted to the hospital because of deepening jaundice, nausea, anorexia and vomiting, and elevated hepatic enzyme levels. Blood determinations for both hepatitis A and hepatitis B surface antigens were negative. She had two episodes of hypoglycemia, with a lowest recorded blood glucose level of 12 mg/dL. During both episodes she responded rapidly to intravenous glucose therapy. She recovered fully from the hepatitis without any residual hepatic dysfunction. Hydralazine and propranolol therapy, which had been discontinued while she was in the hospital, was resumed without recurrence of the hypoglycemia. She died a year later in another hospital from severe hyperkalemia.

RESULTS

Six patients who were treated for hypoglycemia while in a uremic state were included in the study (Table I); all required maintenance dialysis. There were three men and three women, ranging in age from 25 to 91 years (mean age, 48.6 years). The number of hypoglycemic episodes per patient ranged from one in four patients to 10 in one patient (Table I). Measured blood glucose levels during a hypoglycemic episode were less than 25 mg/dL in all patients and were under 5 mg/dL in two patients. Residual renal function, assessed by creatinine clearance, was 5 mL/min or less in all patients. Serum albumin levels were below normal in five of six patients. Propranolol had been administered to four patients on the day of a hypoglycemic episode. Hypoglycemic episodes were not related to meals or dialysis.

DISCUSSION

Hypoglycemia complicating uremia therapy can be a life-threatening condition. In these patients, the differential diagnosis of a sudden deterioration in mental status from alertness to a comatose state suggested either an intracranial catastrophe, such as subdural hematoma, or an abrupt metabolic change. While pursuing alternative diagnoses, the first therapeutic (and diagnostic) step was the intravenous infusion of hypertonic glucose solution. With the exception of patient 1, all patients responded promptly and completely to glucose administration.

Glucose intolerance manifested by fasting hyperglycemia and a glucose tolerance test result compatible with diabetes

TABLE I. Characteristics of Patients with Uremia and Hypoglycemia

Patient	Age/Sex	Diagnoses	Year Maintenance Hemodialysis was Begun	Therapy*	No. of Episodes of Hypoglycemia	Lowest Recorded Blood Glucose Concentration, mg/dL
1	91/M	Nephrosclerosis, septicemia	1979	Digoxin, methyldopa, disopyramide	10	18
2	73/M	Obstructive uropathy, bacterial pneumonia	1980	Penicillin, dexamethasone	2	21
3	25/M	Glomerulonephritis, hypertensive encephalopathy, acute upper gastrointestinal bleeding	1980	Propranolol, clonidine	1	13
4	34/F	Malignant hypertension	1980	Propranolol, clonidine	1	3
5	25/F	Glomerulonephritis, cardiac arrest, severe hyperkalemia	1975	Propranolol	1	1
6	34/F	Glomerulonephritis, non-A, non-B hepatitis	1980	Propranolol, hydralazine	1	12

* All patients also received $Al(OH)_3$ and folic acid.

mellitus is present in the majority of nondiabetic patients who become uremic.[1,20,21] However, the exact underlying mechanisms are not clear. The mechanism of uremic toxicity or uremic glucose intolerance may be caused by the following: (1) accumulation of indoles, guanidines, phenols and aliphatic amines,[1,21] and parathyroid hormone[22]; (2) peripheral resistance to insulin action[1]; (3) decreased turnover of and increased sensitivity to the glucose-elevating effect of glucagon[21]; (4) potassium deficiency[1,20]; (5) parathyroid hormone-induced, accelerated glucose formation[21]; (6) an unquantified effect of raised levels of prostaglandins, gastrin, and growth hormone.[1,20,21] Inspection of this abbreviated list of glucose-elevating stimuli indicates the complexity of the biochemical perturbations that occur in patients with uremia.

Why then is hypoglycemia recognized with increasing frequency in uremic patients? Each of the factors enumerated above is bidirectional and, if upset, could alter the delicate balance between glucose production and utilization, resulting in hypoglycemia. Impaired muscle metabolism, for example, could reduce the synthetic rate of gluconeogenic amino acids.[21] Pyruvate uptake by the liver is delayed in patients with uremia, suggesting that its conversion to phosphoenol pyruvate, a key glucose precursor, might also be inhibited.[10]

An analysis of the common factors that might have instigated hypoglycemia in these six patients suggested two likely possibilities: hepatic glycogen depletion and propranolol toxicity. Glycogenolysis is the primary mechanism by which a falling plasma glucose concentration is corrected.[1] In the presence of hepatic damage from any cause, hepatitis for example, glycogen stores in hepatocytes are reduced, and the release of glucose in response to hypoglycemia is muted. Severe liver disease was found in five of the six patients, as shown by their low serum albumin concentrations. Drugs known to induce hypoglycemia had been administered to five of the patients on the day hypoglycemia was observed; four patients received propranolol, and one took disopyramide. Both drugs are thought to impair carbohydrate metabolism by increasing peripheral glucose utilization, interfering with gluconeogenesis and blocking glycogenolysis.[16,18,19]

What we infer from these six patients is that hypoglycemia in nondiabetic patients receiving maintenance hemodialysis for irreversible uremia is neither rare nor necessarily of a single cause. The contributory role of propranolol, however, merits special note. The most prevalent predisposing pathogenetic sequence appears to be that of hepatic insufficiency related to uremia, in addition to a superimposed hepatic stress which, in this series, was provoked by propranolol in four of six patients. It was possible in all but patient 1 to correct the hypoglycemia by administering dextrose intravenously, which is the treatment of choice. Death related to hypoglycemia occurred only in patient 1, yielding a death rate of 17%. It seems gratuitous to advise that poor nutrition be avoided in all patients receiving dialysis. Further information needs to be collected on the circumstances, if any, in which to avoid prescribing propranolol. A reevaluation of the prescription of propranolol in the setting of uremia merits further attention.

Acknowledgment. This study was supported in part by a research grant and fellowship from the National Kidney Foundation of New York and New Jersey Inc.

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The femoral triangle

A potential death trap for the drug abuser

BENJAMIN W. PACE, MD, WILLIAM DOSCHER, MD, IRVING B. MARGOLIS, MD

ABSTRACT. A retrospective analysis of the admissions to a major metropolitan hospital during one calendar year was undertaken to determine the severity of complications of parenteral drug abuse related to route of injection. Fifty-two admissions (94.5%) were recorded for complications secondary to superficial venous injection, 49 patients (89%) with uncomplicated superficial soft tissue infections with a mean hospital stay of 8.6 days, and three patients (5.5%) with prolonged hospital visits for treatment of systemic sepsis which resolved without residual disability. In contrast, three patients (5.5%) had complications secondary to deep venous injection, all via the femoral triangle. Each patient in this last group had life- or limb-threatening complications; there was one death, and residual disability was reported in the two survivors, despite aggressive therapy. We conclude that the complications of parenteral drug abuse via the femoral triangle far overshadow those secondary to superficial venous injection, and that the femoral triangle is a potential death trap for the drug abuser.

(NY State J Med 1984; 84:596–598)

INTRODUCTION

Parenteral drug abuse often involves the injection of potentially contaminated material by non-sterile techniques, resulting in many infectious complications. With progressive sclerosis of the superficial venous system, the addict seeks venous access via alternate routes. During a previous hospital stay, an addict may have observed hospital staff using alternative injection sites or may have been treated with internal jugular, subclavian, or femoral venous puncture and may have continued to use these techniques after discharge from the hospital. In addition, the local "street expert" will, for a price, inject addicts using various techniques for deep venous access. Use of the femoral vein for venous access and the associated complications within the femoral triangle have been reported.[1–8] Although we were always aware of the relative severity of complications associated with deep venous injections, review of recent experiences emphasized the magnitude of the complications and forms the basis of this report.

PATIENTS AND METHODS

The medical records of all patients admitted to the Queens Hospital Center in 1980 and discharged with diagnoses of abscess, cellulitis, bacterial endocarditis, thrombophlebitis, pulmonary edema, pulmonary embolism, pulmonary infection, vascular injury, and sepsis were reviewed to determine which patients had a history of parenteral drug abuse. The records were analyzed to determine the nature of the infectious complication, its relation to parenteral drug use, length of hospital stay, and mortality or residual disability at the time of discharge. Admissions for drug overdose and elective detoxification were excluded.

Case 1. Four days after self-injection of a heroin-cocaine mixture into the left femoral triangle, a 25-year-old woman was admitted to the Queens Hospital Center with sepsis, respiratory failure, and migratory pulmonary abscesses. There was also evidence of cellulitis in the left groin. A diagnosis of septic pulmonary emboli was made. Intravenous antibiotics and general respiratory supportive care were instituted. Venography performed on the third hospital day revealed deep venous occlusion involving the entire left leg, with partial reconstitution at the level of the distal external iliac vein. The following day she underwent surgery to ligate the proximal external iliac vein. Despite continued support, her respiratory status deteriorated further, and she expired on the eighth hospital day.

Case 2. A 39-year-old man who had used parenteral administration of illicit drugs for 20 years was admitted to the hospital two days after self-injection in the right femoral triangle. On admission, he showed signs of infection and of an arteriovenous fistula in the right groin. On the second hospital day, the presence of the fistula was confirmed by angiography, and ligation of the common femoral artery with closure of the fistulous tract to the vein was performed. The infected groin was extensively débrided and treated with moist saline dressings in an open fashion, with

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From the Department of Surgery, SUNY at Stony Brook and the Queens Hospital Affiliation of Long Island Jewish-Hillside Medical Center, Jamaica, New York.

Address correspondence to Dr Doscher, Physician-in-Charge of Vascular Surgery, Department of Surgery, Queens Hospital Center, 82-68 164th St, Jamaica, NY 11432.

slow resolution of the local infection. After surgery non-invasive vascular studies revealed a 50% diminution in the pressure of the right dorsalis pedis artery when compared to the right brachial artery, although there was no evidence of claudication. The patient continued to show signs of systemic sepsis. Acute bacterial endocarditis developed, and the patient remained in the hospital throughout the subsequent year. During this time progressive destructive changes of both the aortic and mitral valves were noted. Valve replacement was not feasible because of continuing bacteremia. At the patient's request, he was transferred to a hospital near his home in South Carolina; he was bedridden with near terminal congestive heart failure.

Case 3. A 50-year-old man who had used parenteral administration of illicit drugs for 20 years was admitted to the hospital with evidence of infection in the left groin, two days after self-injection in the left femoral triangle. On admission he underwent incision and drainage of an abscess in the left groin and was started on antibiotic therapy. The infection failed to improve and, because of continued swelling of the leg, venography was performed, revealing occlusion of the left external iliac and common femoral veins. The veins involved in the septic thrombophlebitis were excised and the wound was débrided. Antibiotic therapy and treatment with moist saline dressings were continued, with evidence of slow healing of the wound. On the 61st hospital day, brisk arterial bleeding was seen from the wound and, on exploration, the patient was found to have a "blow out" of the superficial femoral artery. This was controlled with emergency ligation of the superficial artery, resulting in severe ischemia of the leg. The following day, an iliac-distal superficial femoral artery bypass graft was performed through the obturator foramen, with restoration of good pulses in the dorsalis pedis and posterior tibial arteries. The wound healed slowly, and the patient gradually regained the ability to walk. He was discharged on the 161st hospital day, with moderate to severe swelling of the lower extremity that was only partially controlled with elastic stockings.

RESULTS

In 1980, there were 55 hospital admissions of 51 persons with complications related to parenteral drug abuse. Thirty-five of the patients were men and 16 were women. Forty-nine of the admissions were for abscess, cellulitis, or both, involving the distal portions of one or more extremity secondary to superficial injection. The length of the hospital stay in this group ranged from three to 38 days, with a mean of 8.6 days and a median of eight days. Three admissions (5.5%) were a result of major systemic sepsis secondary to superficial injection. Two of the patients had subacute bacterial endocarditis, and one had pneumonia. The former patients required 51 and 27 days in the hospital, and the patient with pneumonia was hospitalized for 19 days. Upon discharge, they manifested no disability.

In sharp contrast, the three patients (5.5%) who had injected drugs in the femoral triangle all experienced major complications. One patient died, and the other two left the hospital with severe residual disability.

DISCUSSION

Parenteral drug abuse is a serious national health problem. In 1979, the government estimated that more than 700,000 Americans nationwide abused parenteral narcotics.[9] Surgical treatment for consequences of this abuse is common. Persons who abuse drugs frequently seek treatment for soft tissue infections, which result from a combination of poor antiseptic technique, injection of contaminated material, and varying degrees of immunosuppression.[10,11] In a series of 49 patients with soft tissue infections that required admission to the hospital, treatment was most often effective in resolving the infections without major residual disability.

However, more serious complications can occur. Geel-

TABLE I. Deep Vascular Complications of Parenteral Drug Abuse

Authors (year of publication)	No. of Patients	Injection Site	Complication	Outcome
Fromm & Lucas (1970)	5	Femoral artery	Mycotic aneurysm	Two "blow outs" Three excision and bypass operations One above the knee amputation
Pollard (1973)	2	Femoral vein	Thrombosis	Residual edema
		Femoral vein	Suppurative thrombophlebitis	Full recovery
Geelhoed, et al (1974)	3	Brachial artery Femoral artery Femoral artery	Mycotic aneurysms	Unavailable
Yellin (1977)	5	Femoral artery Femoral artery Brachial artery Brachial artery Superior mesenteric artery	Mycotic aneurysms	All full recovery
Weinberg and Pasternak (1978)	1	Antecubital vein	Suppurative thrombophlebitis and septic pulmonary emboli	Thoracotomy and ligation of subclavian vein with full recovery
Lewis, et al (1980)	2	Carotid artery and subclavian artery Carotid artery	Mycotic aneurysms	All full recovery
Berguer and Feldman (1981)	53	Femoral artery	Mycotic aneurysms	17% amputation, 22% graft infection, 2% mortality
Pace, Doscher, and Margolis (1984)	3	Femoral vein	Thrombophlebitis and septic pulmonary emboli	Death
		Femoral artery	Mycotic aneurysm	"Blow out," residual edema post-excision and bypass
		Femoral artery	Arteriovenous fistula	Pre-terminal acute bacterial endocarditis

hoed and Joseph,[3] in a review of the surgical treatment used in cases of drug abuse, noted serious cardiac, pulmonary, gastrointestinal, musculoskeletal, and vascular complications. These included acute and subacute bacterial endocarditis (most often right-sided and secondary to *Staphylococcus aureus*), pulmonary edema, hilar lymphadenopathy, pulmonary infections (including aspiration pneumonitis and septic pulmonary emboli), intestinal pseudo-obstruction, hepatitis, septic arthritis, myositis, and necrotizing fasciitis. Major vascular complications included mycotic aneurysms of the brachial and femoral arteries, peripheral arteritis secondary to hand injections, and local venous and lymphatic obstruction resulting in edema of the extremities. Complications in the neck, chest, and groin regions secondary to deep venous injection were not noted in this series. Multiple complications of attempted deep venous injection have been reported (Table I). Lewis et al[4] described 12 patients, nine of whom had nonvascular complications—hemo- or pneumo-thorax, deep neck abscesses, or paraplegia. Venous complications including suppurative thrombophlebitis, venous insufficiency, and septic pulmonary emboli can occur. Weinberg and Pasternak[6] reported on a patient who survived antecubital vein suppurative thrombophlebitis and life-threatening septic pulmonary emboli treated with median sternotomy, ligation of the subclavian artery, and aggressive supportive care. The patient with septic pulmonary emboli secondary to femoral vein suppurative thrombophlebitis described in this report (case 1) was less fortunate, succumbing to overwhelming respiratory insufficiency.

Mycotic aneurysms involving brachial, subclavian, carotid, and femoral arteries may also complicate attempts at deep venous injection. Yellin[8] reported full recovery in five patients treated with surgery for mycotic aneurysm secondary to drug abuse. In contrast, Fromm and Lucas[2] reported loss of a limb in one of five patients treated for femoral artery mycotic aneurysm. Berguer and Feldman[1] reported on 53 mycotic aneurysms of the femoral artery secondary to drug abuse: all were treated with primary excision of the artery and either simultaneous or delayed vascular reconstruction. A graft infection rate of 22%, an amputation rate of 17%, and a mortality rate of 2% in this study reflect a pessimistic prognosis. Arteriovenous fistula formation is a potential complication of any parenteral injection; however, the formation of an infected arteriovenous connection secondary to drug abuse carries the potential for rapid dissemination of infection, as may have occurred in one of the patients described in this paper.

Although much is known about the complications of drug abuse, little has been documented on the relative risks of deep and superficial venous injections. Our experience with 49 patients who were admitted to the hospital with complications of attempted superficial injection revealed a mean hospital stay of 8.6 days and little or no residual disability. The two more serious complications of superficial venous abuse, pneumonia and subacute bacterial endocarditis, required hospital stays of 27 and 51 days, respectively, but no residual disability was noted. In sharp contrast, attempted deep venous injection via the femoral triangle in three patients resulted in one death and life-threatening complications and permanent disability in the other two patients. Review of the literature further supports the significant risk associated with deep venous injection. Mycotic aneurysms or arteriovenous fistulas of the femoral artery, or both, have a worse prognosis than those located at other sites, as documented by Buerguer and Feldman,[1] and Fromm and Lucas,[5] and as shown in this report. We conclude that attempted drug injection via the deep venous system, especially the femoral triangle, represents a potential death trap for the drug abuser.

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REVIEW ARTICLE

Pharmacologic and epidemiologic aspects of alcohol and cannabis

GABRIEL G. NAHAS, MD, PHD

INTRODUCTION

After tobacco and alcohol, cannabis has become the most frequently used psychoactive drug in the United States. It is customary today to compare cannabis with alcohol, and it is often claimed that cannabis, an illegal drug, is less damaging than alcohol, which is legal, and should therefore be made freely available. However, at the present time and in our society, it is not possible to compare the pathologic effects of alcohol with those of cannabis (hashish, marihuana). While the damaging effects of alcohol on man and society have been documented in Western countries, this is not the case for cannabis. The latter substance, because of its illegal status and high cost, is consumed in much smaller amounts and with much less frequency in the population at large. The human and social effects resulting from cannabis use can only be determined two or three decades after the drug has become socially acceptable and its frequency of use comparable to that of tobacco or alcohol. Meanwhile, on the basis of the known pharmacologic properties of cannabis and of its epidemiologic pattern of use, it should be possible to make certain predictions of what these effects might be.

This paper will attempt to compare the pharmacologic properties and epidemiologic profiles of alcohol and cannabis. On the basis of this information, the abuse potential of these two drugs—their capacity to induce daily intoxication and resulting damage in a population of consumers—might be better assessed.

CHEMISTRY AND PHARMACOKINETICS

Alcohol is the main toxic substance in fermented beverages. It has a simple chemical make-up: C_2H_3OH. By contrast, cannabis smoke contains a mixture of chemicals: the cannabinoids, which are specific to the plant, number 40; and others such as terpenes, steroids, and alkaloids number over 300. But it is for its main psychoactive agent, delta-9-tetrahydrocannabinol (THC), that cannabis is used as an intoxicant. The concentration of THC varies according to the preparation: 1% to 3% in marihuana, 3% to 6% in hashish, and 30% to 50% in hash oil.

Alcohol is absorbed rapidly and totally from the upper part of the gastrointestinal tract after ingestion, and absorption is more rapid when fasting. Cannabis is inhaled. Ohlsson et al[1] have established that 20% of the THC in the inhaled smoke of a cigarette will be absorbed in the blood stream. When cannabis is ingested, bioavailability is lower, on the order of 6%.

The distribution of alcohol and THC throughout the body is quite different: alcohol distributes in total body water and has a volume of distribution of 40 to 50 liters; THC, a fat-soluble molecule, is distributed to fat-containing tissue, where it is sequestered. It has an apparent volume of distribution of 500 to 2,000 liters.

The biotransformation of alcohol is a simple process. Ninety percent of it is oxidized to form acetate, a common metabolite of carbohydrates. Acetate is oxidized to carbon dioxide and water or synthesized into fatty acids. Each gram of alcohol ingested yields 7 calories. Alternately, THC is transformed by successive hydroxylation into psychoactive and non-psychoactive metabolites. This hepatic biotransformation occurs during one passage through the liver.

Elimination of alcohol from the body is a rapid process. Less than 10% is released through the lung and kidney, while 90% is metabolized at the rate of 5 to 10 mL/hour, according to zero order kinetics. A single dose—one drink—of alcohol should be eliminated within 6 hours. THC, which is sequestered in fat, is eliminated slowly following its biotransformation. The half-life of THC is approximately one week, and its complete elimination requires one month—80% via the intestine and 20% via the kidney. Enterohepatic recirculation delays elimination.

Accumulation of THC, approaching micromolar concentrations, occurs in fat tissue, and the liver, lung, and spleen.[2] All cannabinoids, whether psychoactive or not, inhibit DNA and macromolecular synthesis in micromolar concentrations. Studies on rodents indicate that, following multiple administrations, concentrations of cannabinoids in the brain and testis remain in the nanomolar range.[3] These studies also indicate that following a single injection, brain concentration of THC is higher than plasma con-

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Address correspondence to Dr Nahas, Professor, Department of Anesthesiology, College of Physicians & Surgeons of Columbia University, 630 W 168th St, New York, NY 10032.

Based on a lecture given at the Department of Psychiatry, Karolinska Institute, Stockholm, Sweden.

centration.

ACUTE EFFECTS ON THE BRAIN

The main target of alcohol and marihuana is the brain. Their mechanisms of action on central nervous system activity, however, are quite different.

Effects on neurochemical brain mechanisms. The relative simplicity of the action of alcohol contrasts with the complexity of the biochemical effects of THC on brain mechanisms. Ethanol exerts most of its neurochemical and behavioral effects as a result of a physico-chemical action at the surfaces of the neuronal membranes of the brain. This action requires a high concentration of the drug, from 0.2 g/L to 1 g/L (equivalent to 0.5 mM to 2 mM).

The effects of THC are produced with nanomolar concentrations (a million times smaller than needed with alcohol) and are stereospecific: the "trans" form and not the "cis" form is psychoactive. This is characteristic of drugs that act on or near a "receptor site." No specific receptors for THC have been isolated, but this molecule interacts with several neurotransmitters, such as acetylcholine,[4] dopamine, and 5-hydroxytryptamine, and neuropeptides in a fashion that has not yet been elucidated.

Effects of cannabis and alcohol on anxiety and pleasure-reward brain mechanisms. In 1927, Freud stated that "intoxicating substances when present in blood or tissues, directly cause pleasurable sensations, and make one incapable of receiving unpleasurable impulses."[5]

He was one of the first psychiatrists to hint at the existence of specialized brain mechanisms for feelings of anxiety, pleasure, and reward, which were described 30 years later by Robert Heath[6] and other neurophysiologists. According to Heath, alcohol acts to reduce anxiety in the same manner as diazepam, and its consumption is accompanied in man by a reduction of hypersynchronous activity, recorded with electrodes placed in the hippocampus and gyrus. Alcohol also induces a significant increase in the pain threshold.

According to Heath, cannabis has a direct effect on the pleasure-reward system that is characterized by the appearance of slow wave activity in the septal region.

Effects on brain reinforcement mechanisms. The pleasurable effects of alcohol and marihuana consumption lead to positive reinforcement and repeated intake. Alcohol intoxication is associated with unpleasant and sometimes humiliating side effects, which may act as negative reinforcers and enhance therapeutic efforts to promote abstinence. Such negative reinforcement is unusual following marihuana intoxication, which is rarely accompanied by dysphoria or panic reactions. The lack of unpleasant effects associated with marihuana use provides limited motivation for therapy or abstinence.

Effects on cognitive function. Alcohol is a psycho-depressant agent which acts primarily to inhibit the ability of the neocortex to integrate brain signals. As a result, fine grades of discrimination, memory, concentration, and insight are impaired, and there are a release of inhibitions, uncontrolled mood swings, and emotional outbursts with possible blackout of short-term memory.[7]

Cannabis intoxication depresses arousal and awareness. The depressant effect of the drug is accompanied by an increased self-perception of certain sensory stimuli such as music appreciation. An impairment of memory storage (short-term memory) is also evident; this has been related to decreased acetylcholine turnover in the hippocampus.[4]

Both drugs are associated with abnormal sleep EEG patterns and impaired psychomotor performance.

Driving impairment. Whereas plasma levels of alcohol can be determined quantitatively to assess driver intoxication, there is no test to document the level of THC in plasma. The drug leaves the circulation rapidly, dropping to concentrations of a few nanograms/mL in less than an hour, which is not sufficient to establish intoxication.[1]

CHRONIC EFFECTS

The liver. Alcohol, when consumed by an average adult in amounts that exceed 50 mL of pure alcohol a day, has been associated with chronic disease.[8,9] Liver damage is the most common result of prolonged use of alcohol. This organ is the site of transformation of ethanol into acetaldehyde, a much more toxic substance, which is in turn rapidly dehydrogenated into acetic acid. Liver impairment will manifest itself by a decrease in protein synthesis and other symptoms of hepatic failure, which in turn will affect other organs, including the brain. By contrast, THC and other cannabinoids, although transformed in the liver, are not hepatotoxic.

Respiratory function. Although the lung is not the target organ of alcohol intoxication, persons who abuse alcohol exhibit a decrease in pulmonary function and an increased incidence of pulmonary disease. They also tend to be heavy users of tobacco.[10]

By contrast, THC-containing cannabis smoke has a direct effect on the lung, which is well documented in experimental[11] and clinical studies.[12]

Experimentally, marihuana smoke induces malignant transformation in lung explant and impairs pulmonary macrophage function to a greater extent than does tobacco smoke. Clinically, the controlled studies of Tashkin[12] have documented the damaging effect of marihuana smoking on the upper airways: a dose-related decrease in airway conductance and an increased resistance to airflow was observed in a group of young volunteers studied in a controlled environment.

Furthermore, Tennant[13] reported the presence of squamous metaplasia (precancerous lesions) in biopsies sampled from American soldiers stationed in Germany who had smoked hashish heavily for two years. (These positive findings should call into question the conclusions of the *Ganja in Jamaica* report which claims that "heavy cannabis smoking does not adversely affect pulmonary function."[14])

The long-term consequences of these acute and subacute effects of cannabis smoking on the lung are not known. On the basis of experience with tobacco, irreversible lung diseases such as emphysema and carcinoma would require 20 to 30 years to develop and be documented.

Immune system. Persons dependent on alcohol present an overall decrease in body defenses and a marked increase in the incidence of degenerative and infectious morbidity.

No epidemiologic studies to document increased disease due to decreased immunologic surveillance have been performed among chronic marihuana users; they do exhibit an increased number of hypoploid metaphases among their lymphocytes.[15] Issidorides[16] has reported morphologic alterations of pulmonary macrophages, neutrophils and lymphocytes among chronic hashish users. In addition, experimental studies have shown that marihuana or THC, administered parenterally or by inhalation, induces immunologic defects in rodents.[17]

Reproductive function. Prolonged alcohol intake has an adverse affect on male reproductive function. Early effects include a decrease in testicular synthesis and in the secretion of testosterone. Decreased testosterone secretion is compounded by an increase in liver clearance of the hormone. The drop in testosterone levels produces a compensatory increase in luteinizing hormone (LH) secretion from the pituitary.[18] These two effects, a drop in testosterone and a rise in LH, explain the opposite and contradictory results of alcohol consumption: decrease in sexual performance and increase in desire.

The effects of alcohol on female reproduction have not been studied as systematically, but alcohol does not seem to disrupt the reproductive cycle. The damaging effect of alcohol on fetal development, referred to anecdotally throughout the ages, was scientifically documented for the first time in 1968 by Lemoine[19] in France and four years later by Jones[20] in England. The fetal alcohol syndrome is characterized by low birth weight and length, failure to make up the difference in size and weight, small head circumference, anomalous facial features, and mild to moderate mental retardation.[21]

Cannabis consumption also has adverse effects on male and female reproductive function. In the male, experimental and clinical reports have documented that cannabis consumption decreases spermatogenesis and sperm motility,[22] and increases abnormal forms of sperm. In experimental studies, these abnormalities are produced by THC administration or by other non-psychoactive cannabinoids such as cannabidiol. The mechanism of action of THC has been attributed to its central hypothalamic effect; it interacts with the levels of the neuropeptides luteinizing hormone releasing hormone and thyroid releasing hormone.[23] As a result, the pituitary release of LH and follicle stimulating hormone (FSH), which is controlled by these neuropeptides, is disrupted. There might also be a direct effect of THC on the germinal epithelium of the testis.[22]

THC affects non-human primate reproductive function by disrupting LH, FSH, and prolactin production. This results in irregular and anovulatory menstrual cycles.[23] Administration of THC or cannabis extracts is fetotoxic in four animal species tested,[24] including primates.[25] There is also an increased incidence of fetal loss. Surviving neonates are hypotrophic and exhibit abnormal behaviors. Sassenrath[25] concludes that "the pattern of reproductive failure in female primates treated with THC indicates that this drug is toxic to the embryo and fetus, but it is not characterized by any specific birth defect as was the case with thalidomide."

Following these studies, fetal marihuana syndrome, resembling fetal alcohol syndrome, has been described in the United States.[26]

CHRONIC EFFECTS ON BRAIN AND BEHAVIOR

Brain abnormalities and mental illness. Chronic excessive ingestion of ethanol is directly associated with severe neurologic and mental disorders: brain damage, memory loss, sleep disturbances, and psychoses.[27] A decrease in brain size has been documented in chronic alcohol abusers.[28] In addition, nutritional and vitamin deficiencies resulting from poor food intake or impaired gastrointestinal function contribute to brain disease, such as Korsakoff's psychosis.[30]

No similar brain abnormalities have been reported with chronic cannabis users. The only somatic alterations produced in the brain by chronic marihuana exposure have been reported by Heath in primates.[30] These consisted of ultrastructural synaptic alterations with clumping of synaptic vesicles and inclusion bodies in the nucleus of the cell. The clinical significance of such changes, if they occur in man, has yet to be determined. Specific disturbances in behavior and increased incidence of mental illness have been described among heavy marihuana users.[31]

A state of withdrawal, apathy, and indifference, as well as general mental deterioration have been associated with chronic marihuana use, and these symptoms have been given the name of "amotivational syndrome."[32] This apathetic condition has been described by United States high school students as the "burn out" syndrome.

The increased incidence of mental illness caused by cannabis use has been reported throughout the past 2,000 years in historic and medical literature. This mental effect is of the schizophrenic type, and without proper treatment may linger.[1] By contrast, the use of opiates, including heroin, has never been associated with mental abnormalities.

Whether cannabis induces schizophrenia per se or reveals a latent case of the disease is still being debated. It is now generally accepted that subjects prone to this illness may develop a schizophrenic episode as a result of using the drug.[33]

Tolerance and withdrawal. Tolerance—the ability to withstand marked increase in dosage to obtain or maintain the initial effect—develops to both alcohol and cannabis consumption.

Tolerance to ethanol is a metabolic as well as functional reaction. A metabolic response evolves through a microsomal oxidizing system that is induced by the drug and may handle up to 50% of the ingested dose. Tolerance to ethanol is also functional, in that "fluidization" of the neuronal membrane occurs, associated with a change in its lipid composition.[34] The maximum tolerance to alcohol is 1 to 16 times the initial dose (one drink) (24 g to 384 g; the latter may be a lethal dose).[8,9]

Withdrawal symptoms following abrupt cessation of ethanol ingestion in chronic alcoholism include nausea, vomiting, and anxiety, and severe symptoms such as seizures, hallucinations, and delirium tremors.

Tolerance to cannabis develops rapidly. It has a metabolic component and is also functional at the tissue level. THC might cause a "fluidization" of the membrane, which would alter the receptor response to the drug. A chronic user may smoke the equivalent of 500 mg of THC in a day, which would result in a bioavailability of 100 mg. Initially, 5 mg of THC inhaled—1 mg absorbed in the blood—will produce a marked psychoactive effect. Withdrawal symptoms have been reported in subjects who have ingested 200 mg of THC a day for several weeks.[35] These symptoms include nausea, vomiting, sweating, tremors, and sleep disturbances.

Use of multiple drugs. Heavy users of alcohol tend to take psychodepressant drugs such as barbiturates and benzodiazepines, and they are often heavy smokers. The daily use of cannabis has been associated with the use of stronger illicit drugs: Kandel[36] reported in a prospective study among 5,500 high school students that 26% of those who had used marihuana went on to experiment with opiates, barbiturates or amphetamines.

EPIDEMIOLOGIC ASPECTS

A knowledge of the actual rates of consumption of dependance-producing drugs in a population is most useful in order to predict the medical or social risk associated with their use. Such information is fragmentary, except for alcohol.

The French mathematician Ledermann[37] was the first epidemiologist to study the frequency distribution of individual consumption of alcohol in France. His fundamental observation was that diverse frequencies did not occur randomly, but that their distributions could be related as a first approximation to the statistical law known as the normal logarithmic law: the distribution curve is sharply skewed and the average consumption does not divide the population into two equal groups, one consuming less than the average and the other more. In France, the distribution of consumption is roughly two thirds of the population below average and one third above. There was, in fact, covariance between average "reasonable" consumption and excessive "unreasonable" consumption associated with pathology. Ledermann concluded that average and excessive consumption were not independent from each other, and that an increase in average consumption is associated with a rise in excessive consumption. Roughly, the percentage of alcohol abusers in a population of alcohol consumers remains constant between 7% and 9% of the total number of consumers.

Ledermann's model was validated in Canada by De Lint and Schmidt[9] who also suggested that an increase in average alcohol consumption is associated with increases in excessive consumption and related pathology.

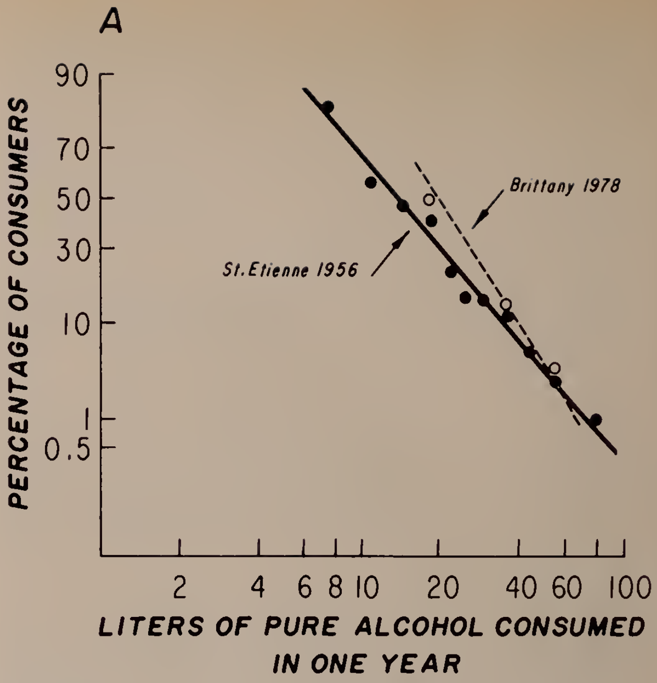

FIGURE 1. The log normal distribution of alcohol consumption in two groups of adult consumers of alcohol in France. One (solid line) studied by Ledermann[23] in 1956 among 440 miners in the St. Etienne area; the other (dotted line) tabulated by Breslow[28] among 775 adults from Brittany.

Smart and Whitehead[38] reported that the consumption of illicit mind altering drugs by Canadian students presented a log normal distribution.

Paton[39] simplified the graphic representation of a log normal distribution by plotting the data on logarithmic-probit coordinates. If one plots on this paper the quantity (or frequency of consumption) of the drug within a given period, and at a given rate or higher, a straight line is obtained if the distribution is normal. The intercept of the curve with a perpendicular passing through the point corresponding to 50% of the population gives the median value, and the slope of the curve gives the standard deviation.

This method has been used to analyze the frequency distribution of alcohol consumption reported by Ledermann[37] and by Breslow[40] (Fig 1). The fitted straight lines, based on a coarse grouping of daily alcohol consumption,

TABLE I. Prevalence of Marihuana Use Among United States High School Seniors[*]

	1975 (9,400)	1976 (15,400)	1977 (17,100)	1978 (17,800)	1979 (15,500)	1980 (15,900)	1981 (17,800)
Percent ever used	47.3	52.8	56.4	59.2	60.4	60.3	59.5
Percent in last 12 months	40.0	44.5	47.5	50.2	50.8	48.8	46.1
Percent in last 30 days	27.1	32.2	35.4	37.1	36.5	33.7	31.6
Percent daily in last 30 days	6.0	8.2	9.1	10.7	10.3	9.1	7.0
Cumulative frequency of marijuana use in the population of users[†]							
1 or more days/yr	84.57	84.28	84.40	84.80	84.11	80.93	77.47
12 or more days/yr	57.29	60.98	62.7	62.67	60.43	55.89	53.10
360 days/yr	12.68	15.53	16.13	13.07	17.05	15.09	11.75

[*] Johnston LD, Bachman JD, O'Malley MP: *Student Drug Use in America, 1975–1980.* National Institute for Drug Abuse, 1981.

[†] Each percentage is the ratio of the students who reported using marihuana at a given yearly frequency to the percentage who reported ever using marihuana. For example, 84.57% for the class of 1975 = 40.0/47.3.

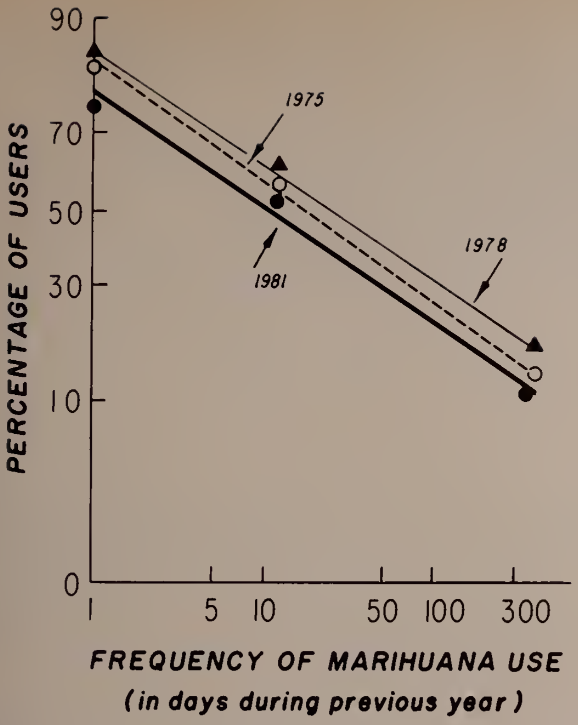

FIGURE 2. The log normal distribution of daily frequency of marihuana use among United States high school seniors.[26]

are very close in both groups and have similar slopes (−1.6 and −1.72).

In this study,[41] data reported by Johnston et al[42] on the prevalence of marihuana use among American high school seniors during the period between 1975 and 1980 (Table I) were plotted on a probability-logarithmic scale to determine if they followed a log normal distribution. The fit was excellent for marihuana consumers during the five years reported. Three of these years are represented in Figure 2. The value of the slope for the class of 1975 is −0.37 and for the classes of 1978 and 1981 it is −0.33.

The percentage of daily users, representing the "at risk" population, represents 13% to 18% of the total number of users. This percentage increases with prevalence of usage.

The slope of the curve for marihuana consumption is not as steep as it is for alcohol, indicating that there will be a greater proportion of daily use—intoxication—in relation to per capita consumption than for alcohol. (For the same population of high school students, the proportion of daily consumers of alcohol was 7% of the total population of consumers.)

The implications of this sociometric model are clear: the availability of marihuana among adolescents is associated with a high incidence of daily use of the drug and resulting intoxication.

Observations made by the author in Jamaica and in Morocco indicate that 50% of the male population between the ages of 15 and 45 years that live in areas of cultivation consume the drug daily. It would appear that the abuse potential of cannabis—its capacity to induce daily intoxication—might be higher than that of alcohol.

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THE MEDICAL AND SOCIAL CHALLENGE OF ALCOHOLISM

Those of us who lived our early lives before the first World War period know that in that period the attitude toward drinking was quite different than following it. Then, it was decidedly not common to feel the need of serving "drinks" at a home gathering. In business the mode was not to "high pressure sales" by way of dinners, drinking, and night clubs. Rather, employees in business were carefully scrutinized as to their drinking habits. In college there were rare beer parties, but a college social function was scandalized by a "lit" college man. A college woman who drank was unheard of and inconceivable. Then came the war and prohibition. The "he-man" rose up in righteous indignation at the challenge to his personal liberties and started to "show the world." He talked and acted so vigorously or belligerently as to make it seem quite effeminate not to show one's "backbone" by carrying a hip flask. Soon the high school children were doing it, as well as college girls and boys. I know even of an instance of a mother who gave her 16-year-old daughter a flask as she was going to a party so that she would not be endangered by poisoned bootleg liquors. The mode spread to locker rooms and bridge tables.

Thus, in a relatively few years I should say, we lost the benefits derived from some fifty or more years of what was really preventive medicine, though it was unfortunately often in the guise of moral or religious propaganda.

All good medical authority recognizes that alcohol in immoderation reduces the efficiency of the individual, as well as dulls his ethical and moral sensibilities, and makes him less and less a social and economic asset. In business he becomes a hindrance to an organization from the changes slowly wrought in his personality before it is recognized. Adolf Meyer phrases it as follows: "Alcohol does much of its harm by its relatively insidious, apparently insignificant effects on the management of individuals and social life. It is difficult to say where the definitely conspicuous effects in the production of clearly pathological consequences begin. The usual effects of alcohólized sociability and their lowering of standards can be more or less covered up and made up for. At any rate, they may disappear in the immediate gain of gratification and joviality and the reduction of tension and any burdensome sense of responsibility, but usually at the expense of ultimate performance and of the family budget and of interest in more far-reaching civic enterprises, of provisions for education, of the cultivation of amusements free from alcohol, and of the general standards of social life." He also says: "Any easy method of escaping responsibility implies a lowering of standards and avoidance of effective solution."

The greater the multiplication of individual instances of alcoholism, the greater the weakening of the social fiber of a community. The wastage in living is intangible and incalculable, but nevertheless positive and lamentable.

EUGENE N. BOUDREAU, MD
(*NY State J Med* 1941; 41:2413)

Restoration of the license to practice medicine

William L. Wood, Jr, Esq, Anthony Z. Scher, Esq

Suspension, revocation, and restoration of medical licenses are matters of serious concern, not only to the medical profession, but to the general public as well. The focus of this communication is on the process of restoration of a medical license in New York State after it has been revoked. This process is a multi-tiered one that protects the public by requiring a careful review of any request for the restoration of a license.

Scope of the Problem

From 1977 through 1983, 113 physicians had their licenses to practice medicine revoked or surrendered their licenses in New York State (Table I).

During the same period of time, however, only 29 of those physicians (25.6%) petitioned for restoration of a license that had been revoked. Of those 29 only 9 (31.0%) were successful. Twelve of the 29 petitions were denied outright; three were abandoned or withdrawn, or the petitioner died; and five are still pending (Table II).

Table III shows the total number of petitions filed, covering all of the 30 professions licensed by the Regents for the years 1977 to 1983. Of a total of 100 petitions filed during this period, 32 were granted, 38 were denied, and 22 are still pending. The Medicine and Pharmacy professions have filed the most petitions, 29 each. It is interesting to note, however, that 62,870 physicians are licensed to practice in New York State, but there are only 17,528 licensed pharmacists. By contrast, there are 206,539 registered nurses and 65,788 licensed practical nurses in the state.

Millions of dollars have been invested by and on behalf of physicians in obtaining medical educations. Each physician spends many years acquiring experience and expertise. When a physician's license is revoked, is society thereafter to be denied the benefits of his or her knowledge and skill? Does the physician forfeit all the advantages and rewards that are associated with the practice of medicine?

The answer is no. A license, once revoked, can be restored. It might be assumed that most physicians who have had their licenses revoked would apply for restoration at the earliest possible moment. The economic motivation is self-evident. And, in most cases, being a physician means a lot more than money. Professional life, social life, and family life may revolve around one's status as a physician. Psychological factors are also involved. But, as shown in Table II, very few physicians in New York State whose licenses have been revoked ever apply for restoration. This phenomenon is difficult to explain. Some obtain licensure in other states, and some pursue other careers. However, there may be some who do not apply because they are not aware of their right to do so, or because they are intimidated by the requirements for regaining a license.

The Restoration Process

When a physician is suspended from practice for a month, or a year, or even five years, he knows that when that time is up he will be permitted to resume practice. At the end of that period he does not have to file a petition or ask for permission to practice and he does not have to give anyone notice.

Revocation, however, is quite a different matter—it is for an indefinite period of time. Unless the physician petitions for restoration and is in fact restored to practice, revocation is forever. Even when things go well, the restoration process can take as long as two years to complete.

The New York Education Law provides that "The Board of Regents may . . . restore a license which has been revoked."[1] Section 24.1 of the Rules of the Board of Regents set forth the procedure for the restoration review process.[2] First, the petition for restoration may not be filed with the Education Department's Division of Professional Licensing Services until the order of revocation has been in effect for at least a year.[2] After the petition is filed, the Department's Office of Professional Discipline initiates an investigation. Though each investigation is tailored to the conditions of the particular case, the investigation almost always involves an interview with the petitioner, interviews of character references, a check with law enforcement agencies, and an effort to ascertain what rehabilitative efforts have been undertaken by the petitioner to preclude the kind of behavior that resulted in the original revocation. The Office of Professional Discipline also seeks to learn whether or not petitioners have maintained their professional skills.

The Peer Review System

An Investigation Report, prepared by the Office of

From the Office of Professional Discipline, New York State Education Department, New York.

Address correspondence to Mr. Wood, Executive Director, Office of Professional Discipline, New York State Education Department, 622 Third Ave, New York, NY 10017.

TABLE I. **Medical Licenses Revoked or Surrendered in New York State, 1977–1983.**

Year	Number Revoked or Surrendered
1977	14
1978	11
1979	15
1980	8
1981	11
1982	24
1983	30
Total	113

TABLE II. **Petitions for Restoration of Medical Licenses in New York State, 1977–1983.**

Year	No. of Petitions Filed	Petitions Granted	Petitions Denied	Petitions Abandoned or Withdrawn	Petitions Pending
1977	5	1	1	0	
1978	6	0	1	1	
1979	1	0	1	0	
1980	5	1	5	1	
1981	5	3	0	0	
1982	6	2	2	1	
1983	1	2	2	0	
Total	29	9	12	3	5

Professional Discipline, is then submitted to the petitioner and to a peer panel of at least three members drawn from the New York State Board for Medicine. By having practitioners involved in the earliest stages of the process, the Regents can best ascertain whether or not petitioners have maintained their professional skills. This is an important issue, since the end result of the process may be to permit the resumption of practice.

A petitioner is directed to meet with the peer panel for informal discussions. No formal testimony is taken, and no verbatim record is made. The petitioner has the opportunity to correct, challenge, or supplement anything contained in the Investigation Report. A lawyer from the Prosecutions Division of the Office of Professional Discipline attends the hearing. He does not oppose the petition, but he may question petitioners and raise issues. A lawyer from the Legal Services Division also sits with the peer panel during its conference with the petitioner.

The panel deliberates after each conference and makes a recommendation as to whether or not a license should be restored.

Review by the Committee on the Professions

Copies of a peer panel report are sent to the petitioner and to the Education Department's Committee on the Professions. The committee consists of three Education Department officers appointed by the Regents. After reviewing the peer panel report, the committee calls a meeting with the petitioner. The committee then prepares its report, which includes a recommendation to the Board of Regents as to whether or not the license should be restored.

Review by the Professional Discipline Committee

The Investigation Report and the reports of both the Committee on the Professions and the peer panel are reviewed by the Professional Discipline Committee of the Board of Regents. The petitioner does not appear before this committee. On the basis of the written material, the committee recommends a decision to the Board of Regents. The Board of Regents makes the final decision on restoration at a public meeting. If the petition is denied, the petitioner may ask the Regents to reconsider, may wait a year and then submit a new petition for restoration, or may challenge the Regents' decision in court.[3]

In making its decision the Board of Regents seems to focus on the following question: Would the public interest be served by the restoration of the license? Answering that

TABLE III. **Petitions for Restoration and the Regents' Action, 1977–1983.**

	Petitions Received								Action			
Profession	1977	1978	1979	1980	1981	1982	1983	Total	Granted	Denied	Otherwise Closed*	Pending
Medicine	5	6	1	5	5	6	1	29	9	12	3	5
Pharmacy	10	4	3	5	1	1	5	29	8	14		7
Registered nurses	5	2	1	1	2	2	2	15	3	7	3	2
Licensed practical nurses	1	2	1	0	1	1	3	9	5		1	3
Public accountancy	4	1	1	2	0	1	1	10	5	3		2
Chiropractic	0	0	0	0	1	1	1	3	1	1		1
Dentistry	0	1	0	0	0	0	0	1		1		
Engineering	0	0	1	0	0	0	0	1	1			
Optometry	0	0	0	0	0	0	1	1			1	
Physician's assistant	0	0	0	0	0	1	0	1				1
Physical therapy	0	0	0	0	0	1	0	1				1
Totals	25	16	8	13	10	14	14	100	32	38	8	22

* Otherwise closed: deceased; application abandoned or withdrawn.

question raises at least two issues: Has the applicant been rehabilitated so that the behavior that resulted in the original revocation is unlikely to recur? And has he maintained his professional skills?

Court decisions have given the Regents broad discretion in making restoration decisions. *Jablon versus the Board of Regents*[4] is illustrative of this point:

> In passing upon petitioner's application the Regents exercise a discretion committed to them by the Legislature . . . . The burden is not cast upon the Regents to establish by proof that petitioner's license should not be restored. Petitioner has the affirmative. Upon him is placed the burden, not merely of 'application' but of 'submission to them of satisfactory evidence,' so ineluctable in its implications that it would compel affirmative action from a Board which has 'discretion' to restore or to refuse to restore . . .[5]
>
> The rule is firmly established that the judiciary will not interfere with executive officers in the performance of duties which are discretionary in their nature or involve the exercise of judgment. In the statute under consideration the law reposes discretion in the Regents and not in the courts . . . The courts may not control the discretion of the Board of Regents.[5]

Although the legislature and the courts have given the Regents broad discretion, the Board of Regents appears to have exercised its rights fairly. The Regents seem to recognize the personal and societal investment that has been made by those who have won licensure and seek to restore them to the profession—as long as doing so does not place the public at risk. Perhaps the title of Regent Emlyn I. Griffith's article in the *New York Bar Journal*[6] best expresses the Regents' position: "The Public Comes First in Professional Discipline."

REFERENCES

1. *McKinneys Consolidated Laws of New York*, Annotated, Section 6511.
2. 8 *New York Code of Rules and Regulations*, Section 24.1.
3. *McKinneys Consolidated Laws of New York*, Annotated, Sections 6510(5) and 6510-a(4).
4. 66 NYS 2d 340; 271 App Div 369; See also *Reddick v. Regents* (1969), 297 NYS 2d 339, 58 Misc 2d 970.
5. 66 NYS 2d 343.
6. Griffith EI: The public comes first in professional discipline. *New York State Bar Journal* 1976; 48:100.

FROM THE LIBRARY

REGULATION AND LICENSING OF PHYSICIANS IN NEW YORK

Formal legal licensing of physicians in New York State began in 1891 when the first written examinations were conducted for licensure. This action by New York State preceded by twenty years the report of Flexner on the state of medical education in the United States. Dr. Maurice J. Lewi, of Albany, had been active for a number of years in the legislative activities which led up to licensure laws. His report of early activities has been published in the January 15, 1955, issue of the NEW YORK STATE JOURNAL OF MEDICINE. Having traveled in Europe and having had a keen sense of comparative educational values, Dr. Lewi recognized in the early 1880's that the majority of medical schools were substandard. His account of the historical background of the creation of three separate Boards as of January 1, 1892, is far superior to anything in existence, and the credit for consolidating and amalgamating the three Boards within a few years into one Board of Examiners was for that time a master stroke. . . .

If we look backward for a moment, the period of licensing physicians over the past one hundred and fifty years has been divided somewhat equally between organized medicine and the State. It is an interesting story in which one may look on advances in medical education as the major weapon in improving the relations not only among doctors themselves but among societies, medical schools, and the many people who have administered the formal duties involved in State regulation. The Medical Practice Act cannot be a fixed or a static document, and it will change as do the times, customs, and programs of progress which lie in the future. Licensure as a government operation has had an influence on the quality of medical practice over these one hundred and fifty years, and it considers its position as a membership in the community of interests involved in keeping the standards of medicine at a high level.

STILES D. EZELL, MD
(*NY State J Med* 1957; 57:543–554)

Professional misconduct

JAMES M. MORRISSEY, ESQ

The purpose of this article is to review the law and procedures in New York State when a physician is alleged to have engaged in professional misconduct. Important issues include the definition of professional misconduct, reporting procedures, the investigatory powers of the Department of Health, the procedures followed when a complaint against a physician is found to have sufficient basis to warrant a hearing, and penalties and sanctions invoked when the allegations of professional misconduct are proved to be true.

ORIGIN OF THE MISCONDUCT PROCEDURES

In 1975 the NewYork State Legislature passed Section 230 of the Public Health Law, which set forth procedures to be followed when a physician is suspected of having engaged in professional misconduct. The legislation transferred much of the authority for investigating complaints against physicians from the Department of Education to the Department of Health.

Section 230 was part of a comprehensive bill that sought to address the medical malpractice crisis in New York State by eliminating certain types of lawsuits against physicians and by shortening the time within which a physician could be sued for malpractice. The trade-off for these benefits to the medical profession was the passage of Section 230, which created the Board for Professional Medical Conduct and which strengthened the disciplinary proceedings against physicians. The law was later amended and, among the more important changes were the following: (1) the prosecution of disciplinary cases was transferred from the State Attorney General to the Office of Professional Conduct; (2) minor or technical violations no longer required legal hearings but could be handled administratively; (3) the maximum penalty per specification was increased from $5,000 to $10,000; and (4) hospitals, malpractice insurers, and other health providers were required to report incidents of professional misconduct. Now, several years and many lawsuits later, the full impact of Section 230 can be better understood.

DEFINITION OF PROFESSIONAL MISCONDUCT

Professional misconduct, which is defined in Section 6509 of the Educational Law, includes practicing the profession fraudulently or with gross incompetence or negligence, or practicing with ordinary incompetence or negligence on more than one occasion; practicing while one's ability is impaired by alcohol, drugs, or physical or mental disability; being habitually drunk or dependent on drugs; being convicted of a crime; failing to keep required records regarding controlled substances; refusing to provide services to persons on the basis of their race, creed, color, or national origin; permitting, aiding, or abetting an unlicensed person to perform activities that require a license; and failing to make a report of professional misconduct as required by the Public Health Law.

Examples of misconduct have included practicing acupuncture and fee splitting with an acupuncturist,[1] making fraudulent requests for Medicaid payments,[2] failing to keep records that accurately reflect the evaluation and treatment of patients, guaranteeing that a cure will result from medical services,[3] failing to make available to another physician records prepared for the patient and paid for by the patient, and abandoning or neglecting a patient in need of immediate care.[4]

The bases for professional misconduct are self-explanatory; however, a few points should be expanded on. First, the act constituting professional misconduct need not relate directly to the practice of medicine, but may occur when a physician manifests "moral unfitness" to practice medicine. Thus, pleading guilty to the crime of attempting to bribe a public official, or making improper sexual advances to a nurse has been determined to be misconduct.[5] Second, a physician suspended from practice in another state will, in all likelihood, be suspended in New York State should he or she hold a New York State license.[6] Lastly, physicians may be prosecuted for acts that occurred in the distant past, even more than three years previous to the prosecution.[7]

THE COMPLAINT PROCEDURE

Complaints of professional medical misconduct are made to the State Board of Professional Medical Conduct. The State Board is required by law to investigate any and all complaints; it may also initiate an investigation at its own behest. As a practical matter, however, many inquiries are not investigated: for example, when the facts of the case do not fall within the definition of professional misconduct, or when the violation is marginal at best. Reports may come from patients, doctors, the public, or from health officials. In 1983 there were 819 new complaints, 53% of which originated from the public.

Physicians are required to report to the State Board any information that reasonably appears to show that another physician is guilty of professional misconduct. The only exceptions to this reporting requirement are participation in certain mortality and morbidity conferences (reporting is the responsibility of the chair of such conferences, departments, or committees), or participation in designated programs for the treatment of physicians thought to be suffering from alcoholism, drug abuse, or mental illness. Physicians are not required to violate the physician-patient privilege, and thus are not required to make a report when the information was obtained solely as a result of rendering

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Address correspondence to Mr Morrissey, Morrissey & Thrope, Attorneys at Law, 12 W 37th St, New York, NY 10018.

treatment to another physician. Failure to make such a report about another physician is an independent ground of misconduct, although to date, no physician has been charged on this basis. In 1983 only 4% of the complaints came from physicians.[8]

THE INVESTIGATION PHASE

In 1983 the State Board completed 1,171 investigations, 84% of which were dismissed, and 10% of which went to hearings.[9]

The investigatory powers of the State Board are far reaching and overcome traditional physician-patient privileges. The State Board has subpoena power under which it may require a physician to appear before it and to turn over patient records. The only limitation on this power is that the State Board must make a minimal showing that the complaint against the physician is authentic and of sufficient substance to warrant investigation. Once this is accomplished, the physician's records must be released.[10]

If the director of the State Board, after consulting with a physician member of the State Board, believes that the results of the investigation warrant a hearing, charges against the physician are drawn up, and a hearing is scheduled. However, if the misconduct involves a question of professional expertise, the complaint is referred to an Investigative Screening Committee composed of four physicians and one layperson for a recommended disposition of the matter.

A hearing is conducted by a Committee on Professional Conduct, to consist of four physicians and one lay person, all of whom are members of the State Board, and an administrative officer who has no vote in the final outcome. At the hearing, the State Board presents evidence of the physician's misconduct. The physician has the right to be represented by counsel, the right to produce witnesses and evidence in his or her behalf, the right to cross-examine witnesses who testify on behalf of the State Board, and the right to have subpoenas issued on his or her behalf to require the attendance of witnesses at the hearing.

These rights generally provide the physician with an adequate opportunity to prepare a defense, except in the case of "discovery." Discovery is a process by which, in order to prepare his defense, a person is permitted to probe his adversary's case and to obtain and review data or other materials relevant to the case which are in the other party's possession. It is a lawyer's primary means of preparing a case. Depriving a lawyer of this tool is like depriving the surgeon of x-rays. Yet, neither the physician nor his attorney is allowed discovery at a misconduct hearing.

Thus, the physician would not be permitted to learn prior to the hearing such facts as the following: how the investigation was instituted; the name or names of the complaining witnesses; the contents of the statements of complaining witnesses; the contents of the investigation report that gave rise to the hearing; the names of witnesses who will testify at the hearing; or the documents, reports, records, or other evidence that will be introduced at the hearing.[11] Thus, with the exception of the statement of charges against the physician, which must set forth the material facts upon which the charges are based, the physician will know little about the case.

The legislative view was that professional disciplinary proceedings should be brought on and disposed of with reasonable speed in order to protect the public from possible harm. Thus the discovery device was withheld, a decision that has been upheld in the courts. However, given the already lengthy nature of the proceedings, affording the physician the right of discovery does not seem unreasonable, if the materials are limited to the types described above.

After the hearing, the committee determines which facts have been proven, rules whether those facts constitute professional misconduct, and, if appropriate, recommends sanctions and penalties. These findings, conclusions, and recommendations are reviewed by the Commissioner of Health, the Regents Review Committee, which consists of one member of the State Board and two retired judges, and finally by the entire Board of Regents. Each may substitute its own findings, conclusions, and recommendations.

JUDICIAL REVIEW

Final decisions of the Board of Regents are virtually impossible to overturn in the courts. Since the passage of Section 230, there is not a single reported court decision in which a physician has been successful in overturning the decision of the Board of Regents. Decisions have been attacked because there was not a member of the physician's own specialty on the Committee for Professional Conduct,[12] because a member of the committee was not present while testimony was taken at the hearing,[13] or because the penalty imposed by the Board of Regents was excessive[14]—all without success. Thus, practically speaking, the decision of the Board of Regents is final.

SUMMARY SUSPENSION

Section 230 gives the Commissioner of Health, upon the recommendation of a Committee on Professional Conduct, the extraordinary power to suspend a physician without a hearing, when the commissioner determines that the activities of the physician pose an imminent danger to patients. A hearing must be held within 10 days of presenting the summary order of suspension to the physician. For example, the commissioner has suspended physicians based on allegations that the physician performed unnecessary surgery,[15] that the physician practiced obstetrics in an incompetent manner, especially in relation to home-birthing,[16] or that the physician verbally or physically abused patients. The commissioner exercised this power eight times in 1983.[17]

The extent of the suspension must be limited by the nature of the perceived danger, but the commissioner has the right to suspend a physician from the general practice of medicine. For example, an opthalmologist, alleged to have performed unnecessary cataract surgery, was suspended from the general practice of medicine, not just from performing surgery.[18] The physician suspended for performing home births was barred from practicing obstetrics and medicine in general, after evidence was presented that he had incorrectly treated a patient who had ingested a toxic substance.[19] However, a summary suspension that is thought to be too extensive might be challenged successfully.

A summary suspension may last for no more than 60 days, during which time the hearing described above must take place. A summary suspension may be extended only when the hearing is not completed within 60 days, due to delays initiated by the physician, or, when upon completion of the hearing, the charges against the physician are upheld. Under such circumstances, the suspension is upheld pending the decision of the Board of Regents.

ALTERNATIVE DISPOSITIONS TO MISCONDUCT PROCEEDINGS

A physician who is temporarily incapacitated due to drug or alcohol abuse or mental illness, for example, may voluntarily surrender his license if such incapacity has not caused harm to a patient. The surrendered license may be restored when, upon recommendation of a Committee of Professional Conduct, the Commissioner of Health is satisfied that the physician is no longer incapacitated. A temporary surrender of a license may not later be used against a physician as evidence of misconduct. In 1983, seven physicians temporarily surrendered their licenses.[20]

A physician may also enter into a consent order with the State Board, which must then be approved by the Board of Regents, a procedure similar in concept to "plea bargaining." In doing so, the physician would admit guilt to one or more of the charges or agree not to contest the charges, in exchange for a mutually agreed upon sanction.

DISPOSITIONS AFTER A HEARING

The penalties that may be imposed upon a physician found guilty of misconduct include censure and reprimand, suspension of license with or without special circumstances (therapy, completion of a training course), revocation of license, and a fine. On occasion, the Board of Regents will decide on a penalty and agree to hold it in abeyance subject to good conduct on the part of the physician.

Of the 44 actions taken after hearings in 1983, only two resulted in a dismissal of the charges against the physician. Approximately 65% resulted in physicians losing their licenses, either through surrender or revocation. In addition, eight physicians had their licenses suspended, and three had their licenses suspended with the suspensions held in abeyance.[21]

The State Board has extraordinarily far-reaching powers to investigate complaints of professional misconduct against physicians and to prosecute cases against physicians when evidence is presented to support the complaint. The State Board has near total access to the physician's records, and, in light of the importance of its actions, such powers are appropriate. However, given the very serious consequences that may result from the hearing, the physician should be given access to the material that gave rise to the hearing, as long as that right is not allowed to cause undue delays in the proceedings. Finally, any popular misconception that the State Board favors the physician must be set aside. The State Board, in the discharge of its function to protect the public, does find a great majority of the complaints unfounded. However, when a complaint is found to have sufficient basis to give rise to a hearing, the fact is that most physicians so prosecuted lose their license. Thus, the physician is well-advised to understand thoroughly and to treat with utter seriousness the law and procedure of professional misconduct in New York State.

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4. New York State Department of Health, Office of Public Health, Office of Professional Conduct: *1983 Annual Report*. But see *G. Rehmi, MD et al v Board of Regents of the State of New York*, No. 0226-81 (Sup Ct Albany Co, Dec 10, 1980) wherein the Court declared 8 NYCRR 29.2(a)(6) invalid and stated that a physician's obligation regarding the release of medical records is governed by §17 of the Public Health Law.
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16. *Wootan v Axelrod*, 469 NYS 2d 637 (Ct App 1983).
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18. *John P v Axelrod*, 468 NYS 2d 951 (4th Dept 1983).
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21. *1983 Annual Report*, p 7.

A 39-year-old man with a testicular mass

CASE PRESENTATION

Hiram Cuevas, MD (Third-Year Medical Resident): A 39-year-old motor mechanic was admitted to another hospital because of a non-tender right testicular mass present for two to three months. The patient was otherwise asymptomatic.

Family and past medical history were unremarkable. Review of systems was otherwise noncontributory. The patient had smoked one and a half packs of cigarettes per day for the preceding five years, but had discontinued the habit five months before admission because of a mild persistent cough.

Physical examination revealed a well-developed, well-nourished muscular black man in no acute distress. The patient was afebrile, with a blood pressure of 120/80 mm Hg, a pulse rate of 72 beats/min, and a respiratory rate of 14/min. The skin showed a café au lait area in the right upper quadrant of the abdomen, a keloid on the left flank, and a papular lesion about 3 mm in diameter in the left lower cervical region. Examination of the head, eyes, ears, nose, and throat was not remarkable. Examination of the lungs was negative; the cardiac examination was within normal limits. Abdominal and rectal examinations were unremarkable. A hard non-tender mass, which did not transilluminate, was felt in the upper pole of the right testicle. There was no palpable lymphadenopathy, and the neurologic examination was negative.

Urinalysis done on admission was normal; microscopic examination showed only a few white blood cells per high power field. The hemoglobin was 12.7 g/dL; the hematocrit, 39.2%; white blood cell count, 5,900/mm^3, with a normal differential count; platelet count, 325,000/mm^3; erythrocyte sedimentation rate, 5 mm/hr; reticulocyte count, 1.5%; and the red blood cell indices were within normal limits. The serum calcium was 8.7 mg/dL; phosphorus, 3.3 mg/dL; total serum protein, 6.5 g/dL; and albumin, 3.8 g/dL. Serum creatinine, uric acid, cholesterol, total bilirubin, alkaline phosphatase, lactic dehydrogenase, and glutamic oxalic transaminase were all within normal levels. The prothrombin and partial thromboplastin times were within normal limits. The electrocardiogram was unremarkable.

A chest roentgenogram taken on admission indicated normal cardiac size and shape, clear lung fields, and bilateral enlarged hilar nodes. A computed tomographic (CT) scan of the chest confirmed the bilateral enlarged hilar nodes, as well as the presence of a left paraspinal mass of undetermined nature. The urology consultant advised surgical exploration because of the possibility of a malignant testicular neoplasm. Under general anesthesia, the right testicle was mobilized from the scrotal sac with appropriate tumor precautions. On opening the tunica vaginalis, a 2-cm rounded mass was found to involve the upper pole of the testis and the epididymis. A frozen section of the testicular mass was obtained, and because of the highly suspicious nature of the lesion, the surgeon performed a radical orchiectomy with high ligation of the spermatic cord. The patient tolerated the procedure well.

RADIOLOGY PRESENTATION

John Batillas, MD (Attending Radiologist): The only roentgenograms available are posteroanterior and lateral views of the chest taken a short time after discharge from the hospital (Figs 1, 2). They demonstrate bilateral hilar adenopathy, with some widening of the left paratracheal soft tissues, which may indicate adenopathy in this region. The lungs and costophrenic angles are clear; the heart is normal in size and configuration. I do not see any significant bony abnormality. Spina bifida of the sixth cervical vertebra is noted. There is no evidence of a paravertebral density. A density is present in the dorsal region, but it seems to be continuous with the aortic knob, and I presume that it represents the descending thoracic aorta. The CT scan is not available for review.

CLINICAL DISCUSSION

Lester Blair, MD (Assistant Attending Physician): This patient had a persistent cough that was sufficiently severe to force him to abandon his cigarette smoking habit. He complained of a non-tender mass in the right testicle. Physical examination revealed that the mass was in the upper pole of the right testis, appeared to be separate from the epididymis, and did not transilluminate. There were several skin lesions present. The chest film revealed bilateral hilar adenopathy and a left paraspinal mass.

I would like to begin my discussion by commenting on the skin lesions. The patient had a single café-au-lait spot on the abdomen. Approximately 10% of the general population has café-au-lait spots; when they occur in numbers greater than six, and are larger than 1.5 cm in diameter, the diagnosis of neurofibromatosis is likely. Café-au-lait spots also occur in Albright's disease, but neither of these two entities appear to be relevant to this case. The papular lesion on the neck and the keloid in the left flank are fairly nonspecific findings but may be germane to this patient's di-

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Based on the clinicopathologic conference (CPC) held at the New York Infirmary-Beekman Downtown Hospital, New York, NY, on April 3, 1984. The Summit Medical Group, Summit, NJ, contributed clinical information.

Moderator: Irwin Sharkey, MD, Chief of Medicine; *Clinical Discussion:* Lester Blair, MD, Assistant Attending Physician; *Pathology Presentation:* Solange Abunassar, MD, Attending Pathologist.

Editor: JOHN T. FLYNN, MD

Address correspondence to Dr Flynn, Consulting Editor, *New York State Journal of Medicine*, PO Box 5404, 420 Lakeville Rd, Lake Success, NY 11042.

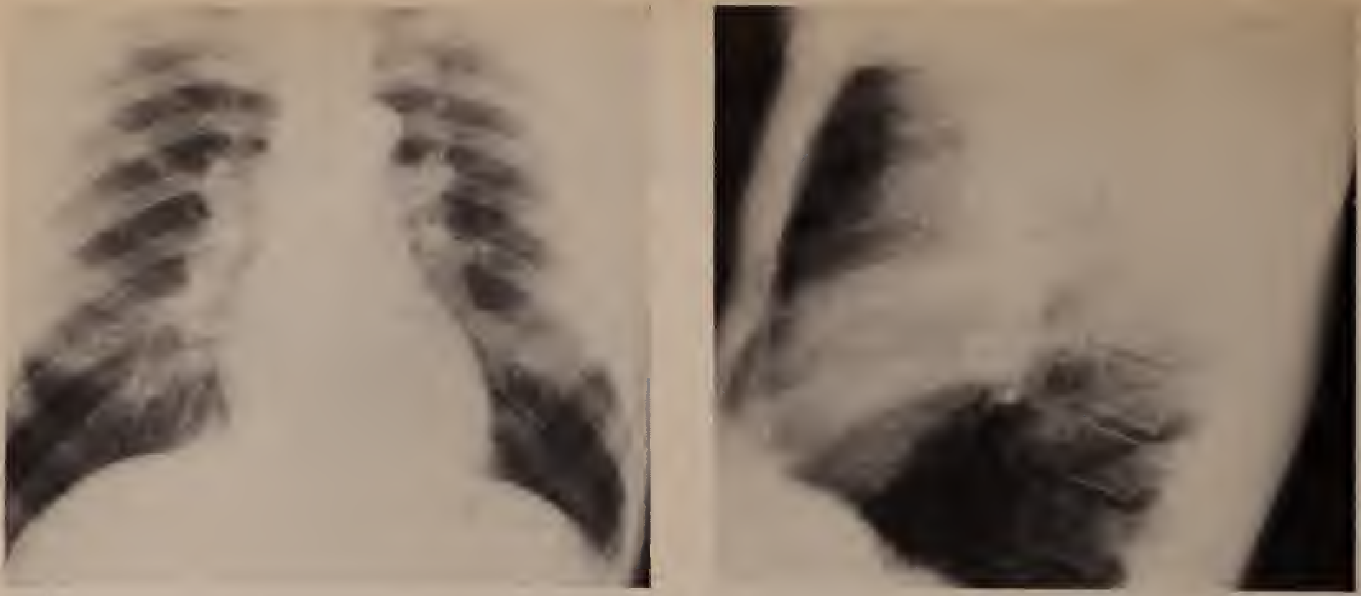

FIGURE 1. Posteranterior (left) and left lateral (right) roentgenographic views of chest demonstrating bilateral hilar lymphadenopathy.

agnosis, and I will refer to them later.

The testicular mass did not transilluminate, so that we can exclude benign masses such as spermatocele and hydrocele. Varicoceles, in which the pampiniform plexus of the spermatic cord is dilated, are usually easy to identify because of their characteristic feel. The veins are usually engorged when the patient stands, and they collapse when the patient assumes the Trendelenburg position.

Primary tumor of the testis must be considered first when discussing a mass such as was seen in this patient. Germ cell tumors comprise about 90% of testicular tumors, with 40% of these being seminomas. The peak incidence of seminoma is between 30 and 40 years of age, and most seminomas occur on the right side. Non-seminomatous germ-cell tumors are divided into four types: embryonal carcinomas, teratoma, teratocarcinoma, and choriocarcinoma. The non-seminomatous tumors tend to occur at an early age, with the peak incidence in the middle of the third decade of life.

The etiology of these tumors is unknown, but it is clear that the incidence is higher with cryptorchidism. Testicular tumors are rare in black men, especially under the age of 65; in a review of 2,688 cases of testicular tumors, only 2% occurred in black patients.[1] Most testicular tumors are painless scrotal masses, associated with a feeling of heaviness in the scrotum; they are firm and smooth and do not transilluminate. These tumors spread through the lymphatic vessels in the spermatic cord. The first nodes that drain the testis are retroperitoneal, and from there the tumor can gain access to the thoracic duct, to the lungs, and to the mediastinum. A patient with a suspected testicular tumor should undergo careful palpation of the supraclavicular area, especially on the left side. Gynecomastia can occur due to secretion of human chorionic gonadotropin, which is usually a bad prognostic sign. Assays for human chorionic gonadotropin and alpha fetoprotein are useful as tumor markers, particularly in the non-seminomatous germ-cell neoplasms. Non-germ-cell tumors are exceedingly rare; they include the interstitial cell tumor and the Sertoli cell tumor. Such patients will often have a feminizing syndrome.

Tumors of related structures in the scrotum may be confused with testicular neoplasia; these include the paratesticular rhabdomyosarcoma, adenomatoid tumors of the epididymis, papillary cystadenoma of the epididymis, and, rarely, a mesothelioma of the tunica vaginalis.

Tumors that metastasize to the testis should also be considered. These usually occur in the sixth to seventh decade of life. One study of these tumors showed that the most common primary tumor forms were bronchogenic carcinoma, adenocarcinoma of the prostate, melanoma, and carcinoma of the kidney, the gastrointestinal tract, and the adrenal glands.[2] Lymphoma can also involve the testis, either as a primary manifestation or as part of a generalized process. Paladugu et al[3] reviewed 38 patients (27 men and 11 women) with gonadal lymphoma. All the patients had non-Hodgkin's lymphoma, and at that time there were only two cases of primary gonadal Hodgkin's disease reported in the literature. The male patients in this series ranged in age from eight to 78 years, with a median of 64 years. Seventy-eight percent of the male patients had a non-tender mass in the scrotum. All of the lymphomas were diffuse, and 75% were of the histiocytic variety. Most patients had evidence of intra-abdominal disease.

Let me now discuss some infectious causes of testicular tumors. Syphilitic gumma used to be a frequent cause of testicular masses, but it is now rare. Gummata tend to appear later in life and usually occur together with a hydrocele. Gummata are usually smooth and hard, with the feel of a billiard ball. Tuberculosis of the testis may occur, usually with simultaneous involvement of the epididymis; the mass is nodular to palpation, and not infrequently is tender. Genital tuberculosis can occur secondary to renal infection or as the result of hematogenous seeding at the time of the primary infection. Other infectious causes to consider would be lymphogranuloma venereum, granuloma inguinale, atypical tuberculosis, coccidioidomycosis, actinomycosis, filariasis, and schistosomiasis; however, inguinal adenopathy invariably accompanies these infections. Wegener's granulomatosis may also involve the genitals.

Sarcoidosis may occur in the testis; Rudin et al[4] in an autopsy series found the incidence of genital sarcoidosis to be 4.5%. Most of the patients were without local symptoms during life. Masses in the scrotum infrequently brought the patient with sarcoidosis to the doctor. These lesions, when discovered, usually required surgical intervention to rule out a tumor. In rare instances sarcoidosis may involve the testicle primarily, sparing the epididymis.

Felson,[5] in his text on chest radiology, mentions several causes of hilar lymph node enlargement. The most common are primary tuberculosis, histoplasmosis, pneumoconiosis, lymphoma, metastatic malignancy, and sarcoidosis. Winterbauer et al[6] reviewed the clinical significance of bilateral hilar adenopathy. In 99 patients with sarcoidosis, 74% had bilateral hilar adenopathy; this disorder was seen in only 9.4% of lymphoma patients, 0.8% of lung cancer patients, and 0.2% of patients with extrathoracic malignancy. Sixty-two percent of the patients with sarcoidosis were asymptomatic on examination; malaise and respiratory symptoms such as chest pain and cough were the most common complaints among the symptomatic patients. Hodgkin's disease involves the hilar nodes in an asymmetric fashion and usually involves nodes at the tracheal bifurcation as well as in the hilar regions. The involved nodes in Hodgkin's disease tend to merge into the cardiac silhouette, whereas in sarcoidosis, they remain distinct. Most patients who have bilateral hilar adenopathy due to diseases other than sarcoidosis are quite sick at the time of presentation; but this patient initially was not obviously ill. An orchiectomy to exclude a diagnosis of testicular tumor was done via an inguinal incision and with the placement of a rubber sheath clamp on the cord to prevent the possible spread of tumor cells via the lymphatic vessels.

This patient could have had any of the lesions that I have mentioned. However, tuberculosis can be excluded on the grounds that the scrotal lesions did not have the characteristic nodular consistency, and because patients with genital tuberculosis commonly have normal chest films. In one series, patients who had genital tuberculosis with abnormal chest films had had roentgenograms consistent with reactivation tuberculosis.[7] Clinically apparent genital tuberculosis does not occur in the setting of primary tuberculosis with bilateral hilar adenopathy. Furthermore, the bilateral hilar adenopathy of tuberculosis tends to be asymmetric.

I am going to exclude lymphoma on the grounds that involvement of hilar nodes and the testis should have been accompanied by more evidence of extensive lymphomatous disease. I would have expected some degree of organomegaly, fever, anemia, and certainly an elevated erythrocyte sedimentation rate.

Of the primary testicular tumors, seminoma would be the most likely cell type; the patient would then have an advanced stage of the disease, by virtue of the hilar node involvement. But this tumor is rare in black patients; furthermore, spread of this tumor to the hilar nodes without disease evident in the retroperitoneum, mediastinum, and lungs would be rare. Tumors can also reach the hilar nodes if the blood stream is invaded—the tumor then spreads to the distal portions of the lung, and thereafter advances via the local lymphatics back to the hila. This form of lymphangitic carcinomatosis is characterized by severe unrelenting dyspnea, which was not evident in this patient.

Sarcoidosis is frequently associated with hilar adenopathy; the disease has a high prevalence among the black population of the United States. Sarcoidosis may also involve the skin to produce papular lesions such as were described in this patient. Granulomas may also develop in preexisting skin scars, to produce characteristic keloids, as were seen in this patient. Hypergammaglobulinemia, which occurs in about half the patients with sarcoidosis, was not present in this patient; the tomograms revealed a left paraspinal mass, we are told, at the level of the aortic arch. In addition to hilar adenopathy, involvement of the aorticopulmonary anterior or posterior mediastinal nodes, or both, is not rare in sarcoidosis.

My diagnosis, therefore, is sarcoidosis involving the testicle, the epididymis, the skin, and the hilar and aorticopulmonary lymph nodes.

Raymond Andronaco, MD (Assistant Attending Surgeon, Department of Urology): Any time I see statistics that report the rarity of testicular tumors among black men, I recall my experience in residency training when a high percentage of patients were black. I believe that such tumors do not represent a disease exclusively of Caucasians. With regard to the diagnostic work-up of the condition, Dr Blair has outlined the process well. In evaluating this condition, even though our suspicions of the presence of a testicular tumor are not strong, we must test for tumor markers—beta human chorionic gonadotropin and alpha fetoprotein. This is one disease in which markers have been successful in identifying the presence of non-seminomatous germ-cell tumors. Any elevation of the serum levels of these two markers is highly suggestive of metastatic disease. These markers can also be used to assess the results of treatment with chemotherapy.

Testicular neoplasm is moving out of the realm of the urologist and into the area of hematology and oncology for patients with metastatic lesions. However, the initial treatment is still high ligation of the spermatic cord and orchiectomy, since chemotherapeutic agents will not affect the primary tumor site. A frozen section was done in this patient, but we cannot rely on the results of frozen sections because of the difficulty in interpreting the tissue.

Essentially, there is no alternative to radical orchiectomy when the surgeon is faced with this disorder. But I wish to reemphasize the importance of securing serum samples for the detection of tumor markers before surgical treatment of the testicle.

CLINICAL DIAGNOSIS

Sarcoidosis involving the right testis and epididymis, the skin, and hilar and aorticopulmonary lymph nodes.

PATHOLOGY PRESENTATION

Solange Abunassar, MD (Attending Pathologist): Two specimens were received by the pathologist at the other hospital. One was a testicular biopsy specimen measuring 1.5 × 0.8 × 0.6 cm from which frozen sections were taken. Routine bacteriologic, acid-fast, and fungal cultures on a portion of the specimen were subsequently reported as negative. The second specimen consisted of testis, epidi-

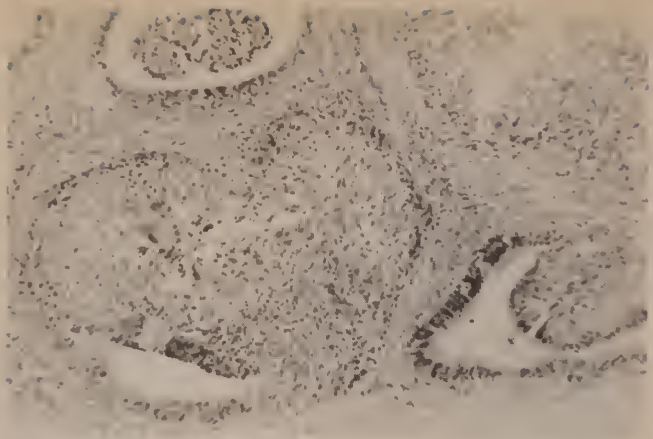
FIGURE 2. Non-caseating granulomas with giant cells between and impinging upon epididymal ducts. (hematoxylin and eosin stain, original magnification × 25)

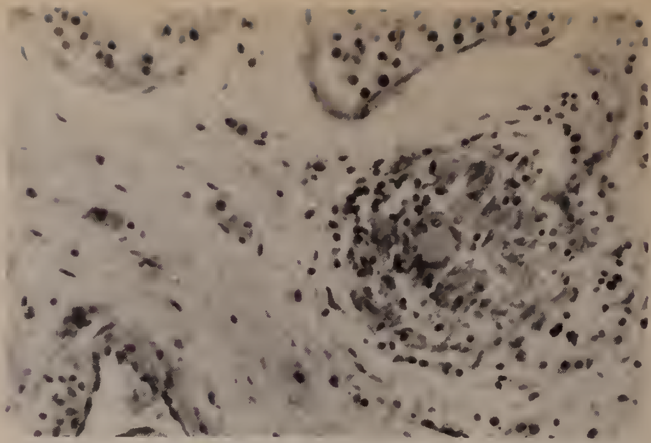
FIGURE 4. Non-caseating granulomas between seminiferous tubules of testis; absence of spermatozoa within tubular lumina, with arrested spermatogenesis. (hematoxylin and eosin stain, original magnification × 42)

dymis, and attached cord. The testis measured 3 cm in diameter and was unremarkable. The epididymis measured 2 × 2 × 2 cm; the cut surface showed a firm tan mass without extension into the testis. Microscopic sections of the epididymis, which we had the opportunity to review, demonstrated non-caseating granulomas primarily between the epididymal ducts (Figs 2, 3), but also within them. In some areas the granulomas were confluent, and there was acute inflammation with destruction of ducts; however, there was no caseation necrosis. In contrast to the epididymis, where granulomas were abundant, the testis contained only a few; the arrested spermatogenesis was more conspicuous (Fig 4). The latter was no doubt the result of obstruction of the epididymal ducts by the granulomas. Stains for acid-fast bacilli and for fungi were negative. There was no evidence of neoplasm. We are therefore dealing with a granulomatous process involving both epididymis and testis. The pathologist's endeavor here is to find the underlying cause or disease entity that evoked this process.

The two most common clinical causes are sperm granuloma and tuberculosis. Negative stains for tubercle bacilli and the absence of caseation do not exclude tuberculosis; negative stains for fungi on the other hand generally eliminate that diagnosis.[8] Sperm granuloma, like tuberculosis, is associated with the presence of spermatozoa in the epididymal ducts; tenderness and a history of trauma or a vasectomy are commonly noted with sperm granuloma. None of the above was encountered here. Other less common causes of granulomatous inflammation of the epididymis and testis are reviewed by Rudin et al.[4] These include sarcoidosis, syphilis, schistosomiasis, filariasis, lymphogranuloma venereum, granuloma inguinale, and Wegener's granulomatosis. Incidentally, a few of the blood vessels in the epididymis in this patient had granulomas (Fig 5); however, this process was non-necrotizing, and there was no other evidence to substantiate the diagnosis of Wegener's granulomatosis. Granulomatous angiitis, on the other hand, has been described in sarcoidosis.[8]

Which of the above granulomatous processes are we dealing with? This often cannot be determined with a biopsy specimen alone; the biopsy results must be compared with other clinical parameters or other laboratory studies. Consequently, the clinical follow-up which Dr Dhalla will present is most important.

Satish Dhalla, MD (Associate Attending Physician): Following discharge from the hospital, the patient initially felt well, except for stuffiness in the nose and throat; in

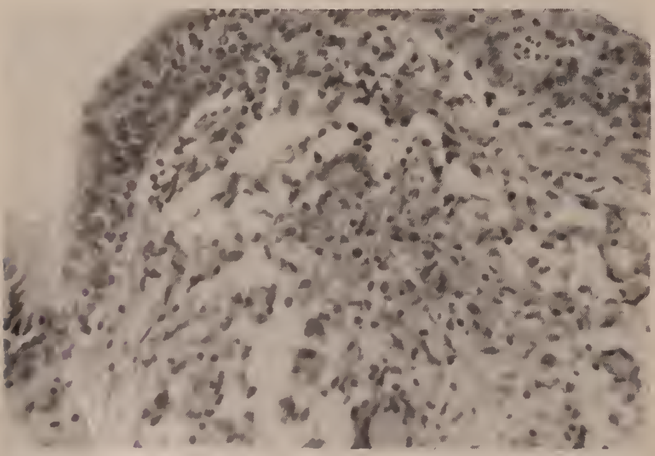
FIGURE 3. Higher-power view of granuloma impinging on epididymal duct. (hematoxylin and eosin stain, original magnification × 42)

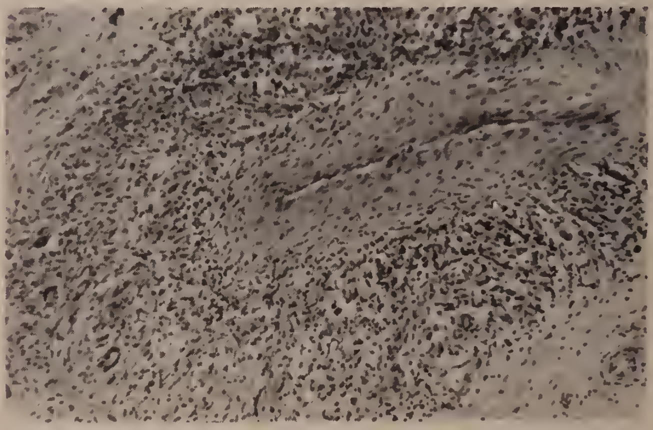
FIGURE 5. Blood vessel within epididymis surrounded and partly involved with granulomatous inflammation. (hematoxylin and eosin stain, original magnification × 25)

addition, mild dependent edema of both ankles developed. The pulmonary consultant to whom the patient was referred found that urine cultures for acid-fast bacilli were negative, and pulmonary function tests were within normal limits.

On follow-up examination during the subsequent four months, chest films indicated progression of the bilateral hilar and mediastinal adenopathy; readmission was advised for mediastinoscopy and biopsy of intrathoracic lymph nodes.

Two weeks prior to the second admission, irritation of both eyes with redness, blurred vision, and photophobia developed; he experienced fever and night sweats approximately every three to four days, but denied exertional dyspnea, increased cough, sputum, or hemoptysis. On the second admission, physical examination revealed swelling of submandibular glands, a 5 × 7-mm nodule in the left lacrimal gland, bilateral synechiae, cloudy anterior ocular chambers, absent right testis, a firm 2.5-cm mass at the upper pole of the left testis, 2+ pitting edema of both ankles, and the skin lesions as previously mentioned. A chest film showed progression of the bilateral hilar adenopathy. Pulmonary function tests were normal, except for minimal reduction in the maximum mid-expiratory flow rate, which suggested some obstruction at the level of smaller airways—with good response to bronchodilators. There was also moderate impairment of carbon monoxide diffusion capacity. Review of the clinical and laboratory findings reinforced the impression of generalized sarcoidosis; mediastinoscopy and lymph node biopsy were thought to be unnecessary. Prednisone, 10 mg four times a day, and steroid eyedrops were prescribed, and the patient was discharged.

Two months later a repeat chest film indicated some decrease in the hilar adenopathy, but there was no change in the size of the left testicular mass; prednisone therapy was continued.

Six months later, the patient was seen by me because of increasing pain in the area of the left testicular mass; prednisone was increased to 40 mg/day, with marked improvement in the left testicular pain and gradual reduction in the size of the mass. After a month of therapy on this higher dose, the medication was gradually decreased to a maintenance dose of 20 mg/day; further attempts to taper the dosage resulted in reactivation of the uveitis.

Two months thereafter, following a burn due to spilling hot water over his right forearm, an extensive keloid developed in that area. The patient refused a skin biopsy of this region. The patient was later unavailable for follow-up. Recently, however, telephone communication indicated that he has done well, is employed full time, is still taking prednisone, 20 mg/day, and remains asymptomatic. The patient also confirmed that at no time during the course of his illness had he been treated for tuberculosis.

In retrospect, the diagnosis of sarcoidosis appears well established on both clinical and pathologic grounds. The mass, which subsequently appeared in the left testis, was attributed to the sarcoidosis and treated as such.

Dr Abunassar: To reiterate, this case illustrates the need for a combination of diagnostic tests to determine that a patient has sarcoidosis. Sarcoidosis is a multisystem disorder, yet genital involvement is uncommon.[9] A review of the literature in 1977 indicated that genital sarcoidosis is more common in black patients, just as is sarcoidosis in general.[10,11] Generally, genital sarcoidosis is preceded for months or years by other symptoms and signs of generalized sarcoidosis, intrathoracic or otherwise.[12] Literature reviews document the rarity of genital sarcoidosis in men and women.[4,9,12–16] Longcope and Freiman[9] outlined the distribution of sarcoidosis throughout the body. The incidence of genital sarcoidosis was 4.5% in autopsy series and 0.5% in clinical practice.[11] However, the incidence may be higher than what is reported, because genital involvement tends to be without symptoms[4] and is rarely associated with a scrotal mass.[17] There are only a few cases in the literature in which sarcoidosis is first identified by a scrotal mass.[10,17–19] Involvement of other areas can be identified on further study of the patient,[12] as was true in this patient, who showed bilateral hilar lymph node enlargement.

The epididymis is the site most commonly involved, with an incidence of 1%.[13] The testis is the next most common site; the spermatic cord, prostate, seminal vesicles, penis, and scrotal skin are less frequently affected.[14,15] However, only 23 cases of epididymal involvement were reported before 1977.[10] When sarcoidosis involves the epididymis, it often appears as a nodular mass, but it can also be diffuse. Sarcoidosis is usually unilateral and less often bilateral.[10] The disease process is usually not painful and can be an acute or chronic disorder; it may be recurrent, often with weight loss[11,19] which may prompt immediate surgical exploration.

Testicular sarcoidosis is rarer than that of the epididymis.[12,15,19] According to Seaworth et al[16] the incidence of involvement of the testis by sarcoidosis is less than 0.2%.[9,11,13] The disease is usually noted at autopsy; on microscopic examination the disorder is identified in interstitial locations in the testis, unlike granulomatous orchitis, which involves the tubules of the testis themselves.[4] Twelve cases of testicular sarcoidosis had been reported up to 1983.[16] One reported case included no microscopic examination findings; in only six patients was the testis clinically abnormal. Four of these six patients had palpable masses during their initial study. All the patients had evidence of bilateral hilar lymphadenopathy.

Thus, we can see why sarcoidosis of the epididymis and the testis can be an enigma to the urologist at the time of operation, when the most prominent differential diagnostic considerations ordinarily would be tuberculosis, sperm granuloma, granulomatous orchitis, and neoplasm.[10] Epididymal involvement by sarcoidosis closely mimics tuberculosis,[4] and testicular involvement is difficult to separate from that caused by a tumor.[14] Scrotal contents may be involved in massive disease, which may result in a conglomerate mass with involvement of the epididymis, often indistinguishable from that of the testis. Although the mass may enlarge to several times the size of the testis, there is usually no fixation of the overlying skin.

In the majority of patients with genital sarcoidosis, the diagnosis is rarely made on the basis of clinical examination, but is established by biopsy or at autopsy.[14] If the biopsy shows granulomatous inflammation, and clinical and other parameters point to sarcoidosis, the need for mediastinoscopy and bronchoscopy are usually precluded.[16] However, the clinical course of the patient must be followed, since the appearance of sarcoidosis in the lung and hilar lymph nodes can mimic cancer. Interestingly, the physician cannot assume on the basis of hilar adenopathy alone that a testicular lesion represents infiltration of the testis by sarcoidosis. Cases of simultaneous testicular carcinoma and intrathoracic sarcoidosis have been reported; furthermore, there are instances of patients with testicular cancer of the non-seminomatous type, in whom intrathoracic sarcoidosis developed during or after completion of therapy for cancer.[20] In this setting the physician cannot assume that the hilar lymph node enlargement indicates metastasis from a primary lesion in the testis. Biopsy of the hilar lymph nodes to show sarcoidosis and not carcinoma would be indicated, thus avoiding the need for chemotherapy. To further complicate matters, regional or generalized granuloma formation in lymph nodes can occur in patients with malignancies.

Management of this disorder varies. Testicular neoplasm often cannot be excluded, and since a surgeon is reluctant to attribute a painless testicular enlargement to a non-neoplastic process without tissue diagnosis, exploration is recommended,[4] with high ligation of the spermatic blood supply to prevent metastasis. A frozen section is performed. If the latter shows granulomatous inflammation, and the clinical picture is that of sarcoidosis, the physician may elect a conservative treatment plan, with steroid therapy and no further surgery. Resolution of testicular sarcoid nodules with steroid treatment has been reported.[15] When the epididymis alone is involved, epididymectomy may be performed without orchiectomy.

If the patient has generalized sarcoidosis and a testicular mass, then improvement following treatment with steroids would indicate sarcoidosis. However, if there is no improvement, surgical exploration of the testis is indicated.[10,15] Others question the usefulness of steroid therapy.[4,16] Some authors advocate orchiectomy, since spermatogenesis is compromised,[14] and because a neoplasm cannot be excluded even in the presence of sarcoidosis.[16] In this case there was no indication that the patient had sarcoidosis at the time of surgery, other than the hilar lymph node enlargement, so orchiectomy was indicated.

In summary, we are dealing with an unusual case of sarcoidosis; the patient initially had both epididymal and testicular involvement by the disease process. According to Schaeffer et al[17] only five patients had been reported prior to 1980 in whom sarcoidosis was initially seen as a scrotal mass.[10,18,19] The clinical significance of genital sarcoidosis derives from its capacity to disrupt gonadal function and its potential to mimic testicular neoplasm.

Irwin Sharkey, MD (Chief of Medicine): Suppose that an internist or pulmonary specialist had suggested that the intrathoracic lesions should be biopsied first, and that the pathology report was one of non-caseating granuloma. How would that have affected the urologist's decision to explore and most probably remove the testis? Would that have supported a judgement not to remove the testis?

Dr Blair: In dealing with a patient who had bilateral hilar adenopathy and who is not very sick, it is a fairly good bet that the patient has sarcoidosis. Other diseases that cause this type of clinical picture will usually present other symptoms and signs as well. Also, as Dr Abunassar said, there can be sarcoid-like granulomas in lymph nodes in conjunction with other tumors, so you have to be absolutely sure what you are dealing with in the testis. This is such a rare form of sarcoidosis, in comparison to the frequency of testicular neoplasms, that given the same patient with the same amount of information and the same initial presentation, I think the surgical approach would have been the same. Most of the experience reported in the literature would confirm that approach. Otherwise one would run the risk of missing a malignant testicular tumor. It might be considered unfortunate for this patient that, in the end, the operation turned out to be unnecessary. However, the greater risk would have been to miss a testicular tumor—especially a seminoma—which could readily be treated, or even a non-seminomatous tumor, if detected and removed in an early stage.

Dr Dhalla: There have been cases reported in the literature in which the testes were not removed, and the patients were treated with steroid therapy alone.[15,18] In response to the steroid therapy, the masses shrink. This approach can be used only in cases where you are sure that the patient has sarcoidosis, based on other findings. Sarcoidosis in another location—identified by biopsy, and followed by the appearance of a testicular mass that diminished in size under steroid therapy, would be a circumstance under which the testicular mass need not be removed.

Dr Blair: If the mass occurs in the setting of an established diagnosis of sarcoidosis, you might be justified in waiting a while and observing the patient during steroid therapy. Nevertheless, you still have to complete the diagnostic work-up, measure the level of the tumor markers, study the patient with an abdominal CT scan, and perhaps consider a lymphangiogram if you are suspicious. Otherwise, you run the risk of missing a treatable tumor.

Dr Sharkey: How long has this patient been followed?

Dr Dhalla: He has done well during the past four years at least. Though I have not seen him during that time, he indicated to me recently that his major problem is the recurrence of the uveitis when the dosage of steroid therapy is reduced.

Joseph Andronaco, MD (Attending Urologist): Dr Sharkey makes an interesting point. If the intrathoracic biopsy had confirmed the presence of a granulomatous or other inflammatory lesion, you would still be obligated to operate because of the presence of a unilateral testicular lesion. The presence of bilateral lesions would have suggested sarcoidosis in this setting. We ordinarily do not biopsy a testicle; if, during surgery a hard mass is found, we remove the testicle rather than biopsy it, since biopsy often is not helpful. If it is a tumor, you are going to have follow-up treatment anyway.

Dr Abunassar was reluctant to diagnose sarcoidosis in the testicular mass, but preferred to call it a granuloma. Would some granulomas with this clinical picture not be diagnosed as sarcoidosis?

Dr Abunassar: Granulomas, together with the clinical picture as described by Dr Dhalla, would be diagnosed as sarcoidosis. However, we have to keep in mind that sarcoidosis and tuberculosis can coexist.[13] The latter, therefore, has to be ruled out. As to reluctance to diagnose sarcoidosis in a testicular mass, let me quote the following from the Seventh International Conference on Sarcoidosis in 1976: "Sarcoidosis is a multi-system granulomatous disorder of unknown etiology. . . The diagnosis is established most securely when clinicoradiographic findings are supported by histological evidence of widespread non-caseating epitheloid cell granulomas in more than one organ, or by a positive Kveim-Siltzbach skin test.”[21] Rosen and colleagues[8] believe that “the pathologist should not render a diagnosis of sarcoidosis based upon examination of biopsy specimens. Neither do [they] feel that the phrase ‘consistent with sarcoidosis’ is useful, since it does not provide any further information, and may even be misinterpreted.” As far as I am concerned, in addition to the above, sarcoidosis is often a diagnosis of exclusion.

Mathia Sukumaran MD (Associate Attending Physician): Was steroid therapy begun immediately after surgical removal of the testis? Once the diagnosis of sarcoidosis is made, steroid therapy should be considered in view of the involvement of the skin as well as the testicle.

Dr Dhalla: The patient was initially referred to an internist following the surgical procedure. The internist was in the process of investigating the nature of the problem; he secured pulmonary function tests and performed tests for tuberculosis and fungal disease. However, I suspect that because the patient was feeling well, he did not return for completion of the tests that the physician had planned. When uveitis, swelling of the lacrimal glands, and fever developed, he returned. On review of the entire clinical picture during the second hospital admission, the mediastinoscopy that had originally been considered was no longer indicated, since the diagnosis on both clinical and pathologic grounds was clearly sarcoidosis.

During the interval between the two hospital admissions the lack of steroid therapy did not appear to have resulted in any significant deterioration of the disease process. In any event, steroid therapy would not have been initiated until the question of tuberculosis as the cause of the condition could have been settled.

Arturo Constantiner, MD (Director, Department of Nephrology): Is there any value to the determination of the serum angiotensin-converting enzyme level in the effort to diagnose this condition?

Dr Blair: The serum angiotensin-converting enzyme level would not be helpful in the differential diagnosis. If it was elevated, that knowledge might help during the follow-up in assessing the degree of activity of the sarcoidosis, but many other conditions can elevate the enzyme level.

John T. Flynn, MD (Associate Chief, Department of Medicine): The question might be raised in this case as to whether the decrease or absence of spermatogenesis might have been secondary to pituitary insufficiency resulting from granulomatous infiltration of the hypothalamus.

Dr Abunassar: Although one cannot be certain without appropriate biopsy and an extensive endocrinologic evaluation, pituitary insufficiency seems less likely in this instance, since there is a local cause in the gonad itself. The absence of spermatogenesis is secondary to obstruction of the epididymal ducts by the granulomatous inflammation, with secondary azospermia or damage to Lydig cells, or both, and secondary infertility.[4] There were no other obvious clinical manifestations of pituitary insufficiency in this patient.

FINAL DIAGNOSIS

Non-caseating granulomatous inflammation of right epididymis and testis compatible with clinical diagnosis of sarcoidosis.

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Spontaneous pneumomediastinum as a consequence of cocaine use

MICHAEL N. BUSH, MD, RICHARD RUBENSTEIN, MD, IRA HOFFMAN, MD, MICHAEL S. BRUNO, MD

Pneumomediastinum (mediastinal emphysema) results from gas entering the mediastinal space. Sources of gas entry into the mediastinum include the deep fascial planes of the neck, the esophagus, tracheo-bronchial tree, pulmonary air spaces, and rarely, the peritoneum. Spontaneous pneumomediastinum is a rare disorder that is not often considered in the diagnosis of pleuritic chest pain. Following is a report on a young man who developed mediastinal emphysema after smoking free cocaine base. The smoking of alkaloidal cocaine involves deep, forced, and prolonged inspiratory efforts with Valsalva's maneuver.

CASE REPORT

A 21-year-old man came to the emergency room complaining of a sore throat, pleuritic chest pain, and dyspnea. The symptoms began one day earlier during an alleged 12-hour session of "free-basing" cocaine. He denied fever, cough, hemoptysis, or trauma. He did not smoke cigarettes, and there was no history of bronchopulmonary disease. On examination, his blood pressure, temperature, heart rate, and respiratory rate were within normal limits. The nose and throat showed no inflammation or hemorrhage. The lungs were clear to percussion and auscultation. Heart sounds were unremarkable, and the chest was not tender to palpation. Hamman's sign was absent. The abdomen was not distended and there was no tenderness. A chest roentgenogram showed free air in the mediastinal space and fascial planes of the neck (Fig 1). The patient was admitted to the hospital. Arterial blood gas levels, an electrocardiogram, complete blood count, and blood chemistry studies were within normal limits. An esophagram was performed; it showed no evidence of perforation or other abnormality. The patient was treated with supplemental oxygen, and his pulmonary status remained stable. There was a gradual decrease in pain and dyspnea, and the patient was discharged two days later with partial resorption of the mediastinal emphysema.

DISCUSSION

Spontaneous pneumomediastinum is an uncommon disorder which occurs as a consequence of alveolar rupture when there is a sudden rise in intra-alveolar pressure, often in persons with normal lung parenchyma. This mechanism was first postulated by Macklin and Macklin[1] in 1944. They suggested that alveolar rupture leads to pulmonary interstitial emphysema with subsequent passage of air along the vascular sheaths and fascial planes into the mediastinum and subcutaneous tissue of the chest and neck.

Common clinical settings for spontaneous mediastinum include asthma, parturition, and violent coughing. The three most common symptoms are pleuritic chest pain (in 82% of patients), sore throat (72%), and dyspnea (54%).[2] On physical examination, subcutaneous emphysema and wheezing are frequently found. Hamman's sign is the most striking clinical sign when it is present, and is described as a crunching sound heard over the precordium. A chest roentgenogram is the most revealing diagnostic procedure; it may show a rim of air along the mediastinum and free air in the fascial planes of the neck.

The critical aspects of management relate to recognition and proper diagnosis. It is important to differentiate spontaneous pneumomediastinum from pneumomediastinum that arises from a ruptured esophagus or large airway. A ruptured esophagus requires emergency repair. Large tears in the trachea or bronchi usually need surgical repair,[3] whereas small tears may be managed by tracheostomy alone. The treatment for spontaneous pneumomediastinum is conservative: treatment of underlying disorders such as asthma, bronchitis, or diabetic ketoacidosis is essential, and supplemental oxygen may be given to relieve respiratory distress and to increase the resorption of nitrogen.[3,4] Pericardial tamponade and airway compression are rare complications of

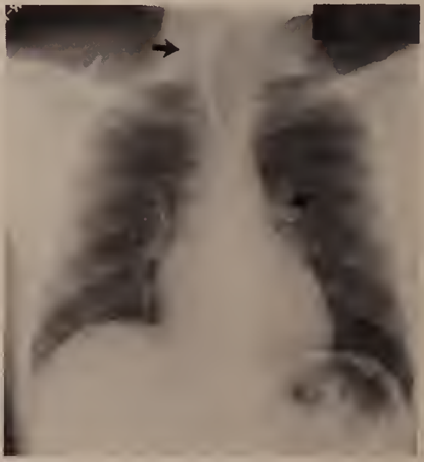

FIGURE 1. A posteroanterior radiograph of the chest showing a rim of air along the left heart border and interstitial emphysema in the subcutaneous tissue of the neck (arrows).

From the Department of Medicine, Lenox Hill Hospital, New York, NY.

Address correspondence to Dr Bush, Assistant to the Director, Department of Medicine, Division of Ambulatory and Consultative Medicine, Lenox Hill Hospital, 100 East 77th St, New York, NY 10021.

spontaneous pneumomediastinum and are treated by pericardiocentesis and tracheostomy, respectively.[4]

It is likely that the patient presented in this report developed a spontaneous pneumomediastinum as a consequence of increased intra-alveolar pressure while "free basing" cocaine.

"Free basing" is a term that is used to describe the illicit smoking of cocaine base.[5] Illicit cocaine is most commonly administered through the nose ("snorting"), but recently there has been an increased number of individuals who smoke alkaloid cocaine. Cocaine base may be "freed" from its hydrochloride salt by treating the cocaine with a basic solution and filtering the precipitate. The cocaine base is usually smoked in water pipes designed for this purpose. The smoke is inhaled deeply and for as prolonged a time as possible, often accompanied by Valsalva's maneuver.

A very intense euphoric state is obtained within two minutes, and, in one study, psychological and cardiovascular effects were equal to or greater than a similar amount of intravenous cocaine.[6] The same study demonstrated a more intense craving for an additional dosage of smoked cocaine than for intravenous cocaine. The euphoria is short-lived, and, in order to maintain this state, the cocaine is smoked at frequent intervals. "Free basing" sessions often last for many hours, as in this case report.

Spontaneous pneumomediastinum has been reported in association with both marijuana[7] and cocaine[8] smoking. Other medical problems related to cocaine smoking include burns and a diminution in carbon dioxide diffusing capacity.[9] As the prevalence of cocaine smoking increases, medical problems that result from this practice may increase in a similar manner.

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See also p 587.

Pneumothorax, pneumomediastinum, and pneumopericardium following Valsalva's maneuver during marijuana smoking

RICHARD B. BIRRER, MD, JOSE CALDERON, MD

Mediastinal emphysema following repeated, prolonged Valsalva's maneuvers has been documented during parturition, emesis, and coughing.[1,2] Although pneumomediastinum secondary to breath-holding during marijuana smoking, in order to increase the drug's effects, has been reported,[3,4] the complication of pneumopericardium has not been recorded previously.

CASE REPORT

A 30-year-old man was brought to the psychiatric emergency facility because of unusual behavior for one and a half week's duration, consisting of uncontrollable screaming, loitering, and an inability to maintain personal hygiene. A diagnosis of acute paranoid schizophrenia was made. The patient also complained of pain in the center of his chest; a pericardial rub was noted on physical examination. An electrocardiogram revealed no abnormalities. A tentative diagnosis of pericarditis was made.

The patient was referred to the medical emergency service. Further questioning revealed that the patient had had a sore throat, chest discomfort, and dysphagia of four days' duration. He described the pain as being dull, non-radiating, non-pleuritic, intermittent—lasting for several minutes to hours, and worse when standing. He admitted to performing Valsalva's maneuver—exhalation against an incompletely pinched nose—while smoking marijuana, as part of a religious cult practice. He denied experiencing shortness of breath, dyspnea, nausea, vomiting, trauma, coughing, hemoptysis, or other cardiopulmonary symptoms, as well as intravenous drug use.

On examination blood pressure was 125/80 mm Hg; heart rate, 82 beats/min; temperature, 36.5°C; and respiratory rate, 12/min. No pulsus paradoxus was identified. The lung fields were clear and resonant; the point of maximal impulse was in the fifth left intercostal space. There was a sound resembling "Rice Krispies," more pronounced during systole and synchronous with each heart beat (Hamman's sign), and bilateral anterior, cervical subcutaneous emphysema was noted. A complete blood count and chemistry study results were within normal limits. A chest roentgenogram was remarkable for the presence of a small amount of air in the left hemithorax, along the left border of the heart, and within the mediastinum and lower cervical region (Fig 1). A diagnosis of pneumopericardium, pneumomediastinum, and subcutaneous emphysema, presumably secondary to a Valsalva's maneuver, was made. Treatment included bed rest and haloperidol therapy. The patient's uncooperative nature prevented barium swallow studies, esophagoscopy, and follow-up chest films. After three days, his condition had improved; he was moved to the psychiatric service.

DISCUSSION

Free air in the mediastinum or peri-

From the Department of Family Practice, SUNY Downstate Medical Center, Kings County Hospital Center, Brooklyn, New York.

Address correspondence to Dr Birrer, Assistant Professor, Department of Family Practice, SUNY-Downstate Medical Center, 450 Clarkson Ave, Brooklyn, NY 11203.

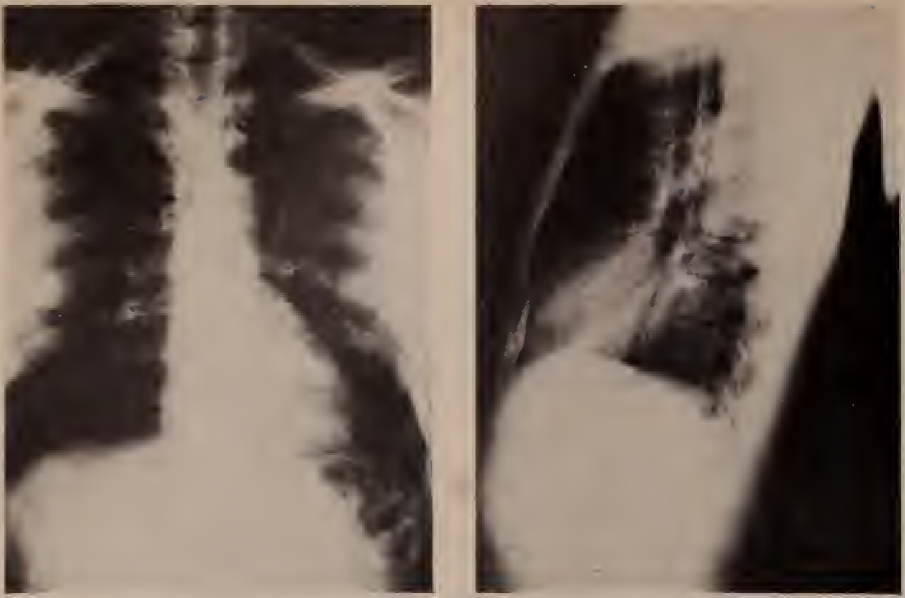

FIGURE 1. Left, posteroanterior view of chest roentgenogram showing right subcutaneous emphysema (long arrow), pneumopericardium (medium arrows), and pneumomediastinum (short arrows); Right, lateral view showing pneumomediastinum (long arrow) and pneumopericardium (short arrow).

cardium, termed pneumomediastinum (or mediastinal emphysema) and pneumopericardium, respectively, are rare entities that are typically self-limiting and benign. Pneumomediastinum, in particular, tends to occur in healthy young men, commonly with no apparent precipitating cause. Forty to 50% of such cases occur in women, and these occurrences have been linked to the Valsalva's maneuver, which is important in the termination of Stage II labor.[1,2]

There must exist a pressure gradient between the alveolus and the surrounding tissue in order for air to pass between them.[5] Obvious causes for such air leakage include direct chest trauma, perforation of the trachea, bronchus, or esophagus, or inflammation of the alveolar wall as would occur in pneumonia, asthma, or emphysema. For the most part, however, the cause of the rupture is difficult to establish. Presumably, in the absence of anatomic defects, possible pathogenic mechanisms may include elevated pressure due to over-inflation of the lung (caused by asthma or emphysema), or an increase in intrapulmonary pressure (due to Valsalva's maneuver, coughing, or emesis), or decreased pulmonary circulation.[6]

Once rupture occurs, air enters the perivisceral connective tissues (causing pulmonary interstitial emphysema), passes through the visceral pleura (resulting in pneumothorax),[7,8] and proceeds along the path of least resistance via the vascular sheaths to the hilus or directly through the mediastinal pleura (leading to pneumomediastinum). The air gradually passes into the subcutaneous tissues of the neck from the mediastinum. Theoretically, air can pass through the great vessels and enter the pericardium through a defect in the serous layer of the parietal pericardium or visceral pericardium.[8,9] It is presumed that interstitial emphysema is associated with air surrounding the cardiac border.[10]

Miller et al[3] and Mattox[4] have reported on 16 patients with pneumomediastinum associated with marijuana smoking.[3,4] Shesser et al[11] have documented pneumomediastinum and pneumothorax resulting from Valsalva's maneuver following cocaine inhalation. The mediastinal emphysema was presumed to be secondary to increased intra-alveolar pressure caused by Valsalva's maneuver. No lung disease was apparent from the physical examination or on roentgenograms.

In the patient described here, it would also appear that the Valsalva's maneuver produced elevated intrapulmonary pressure in the absence of detectable pulmonary disease; an alveolus bordering the heart then ruptured leading to pneumomediastinum and pneumopericardium.

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See also p 587.

Value of computed tomography in treatment planning and follow-up of dysgerminoma

J. POLLACK, MD, D. NORI, MD, B. S. HILARIS, MD

Computed tomographic (CT) scanning of the abdomen, to evaluate the retroperitoneal area, was used in addition to a lymphangiogram in designing the treatment plan for a young woman with stage III pure dysgerminoma of the ovary. In this patient, it was noted that CT scanning was able to provide information on the extent and bulk of retroperitoneal node involvement not available from a lymphangiogram.

CASE REPORT

A 19-year-old woman was seen at Memorial Sloan-Kettering Cancer Center in July 1980, with the complaint of a mass in the left lower quadrant that had been enlarging gradually during a period of one and a half months. The patient had experienced episodic aching in the left flank and irregular menses with variable flow for three months, in contrast to prior normal menstruation. On examination, a 20 × 15-cm mass in the left flank and left lower quadrant was palpated; findings from the rest of the examination were unremarkable. Results of laboratory studies included normal complete blood cell count, liver functions, electrolyte levels, and chest roentgenogram; an intravenous pyelogram demonstrated a left-sided pelvic mass indenting the bladder.

The patient underwent exploratory laparotomy, left salpingo-oophorectomy, and right oophoropexy with wedge biopsy; peritoneal washings were taken and several involved para-aortic nodes were marked with surgical clips.

Surgical findings were as follows: a left ovarian tumor measuring 18 × 13 cm with intact capsule; grossly normal right ovary and tubes; grossly normal uterus, visceral surfaces, liver, and peritoneum; and bilateral involved para-aortic nodes.

Three large nodal masses were noted: there was a right retroperitoneal nodal mass at the level of the second and third part of the duodenum which was marked with clips; a left retroperitoneal mass at the level of the celiac axis which was not clipped; and another left-sided retroperitoneal mass just above the level of the left kidney, extending toward the splenic hilum, which was also clipped. The patient's postoperative course was uneventful, and she was discharged one week after the operation. She was scheduled to receive radiation therapy as an outpatient.

Pathologic findings of the tumor were pure dysgerminoma (Fig 1) of the left ovary, with a normal right ovary biopsy specimen, and normal left tube and peritoneal washings. A postoperative lymphangiogram (Fig 2) confirmed the presence of massive para-aortic node disease, with almost complete replacement of the nodal structures up to the level of the cisterna chyli; no dye was visible beyond the L-3 vertebra. A liver scan taken after surgery was within normal limits.

Because the bulk of the retroperitoneal disease was not well defined by either the surgical clips or the lymphangiogram, a CT scan of the abdomen was obtained before initiation of radiation therapy (Fig 3). The scan showed multiple lobulated masses that represented enlarged nodes at the level of the celiac axis, with pronounced enlargement at the level of the left renal hilum and spleen that was greater on the left than on the right. Initially, the plan had been to treat this patient first with para-aortic and pelvic irradiation, then mediastinal and bilateral supraclavicular node irradiation, and, last, to provide a boost to the area of bulky nodal disease. Because of the unexpectedly large size and extent of the nodal disease, which neither surgery nor the lymphangiogram defined, the radiation therapy treatment plan was modified significantly. The large size of the nodes placed the entire abdominal cavity at risk; therefore, whole-abdomen irradiation was given, followed by pelvic and para-aortic irradiation.

The details of treatment are as follows: whole-abdomen irradiation was given using a 41.5 × 18.5-cm anteroposterior-posteroanterior field, 1,960 rad in 18 fractions (with appropriate kidney blocks used throughout treatment) with 6-Mev photons. After two weeks rest, the patient received combined para-aortic and pelvic irradiation using an "inverted-T" anteroposterior-posteroanterior portal. A dose of 2,200 rad was delivered in 11 fractions with 6-Mev photons from a linear accelerator. After another two-week rest period, the patient received irradiation to the mediastinum and both supraclavicular areas totaling 2,000 rad in 10 fractions via 20 × 12-cm anteroposterior-posteroanterior ports, again using 6-Mev photons.

The patient experienced no major side effects from the treatment. Three months after therapy a CT scan of the abdomen showed marked reduction in the size of the para-aortic adenopathy (Fig 4). On the basis of this finding and the patient's clinical status, we believed that consideration of further therapy, specifically chemotherapy, could be deferred.

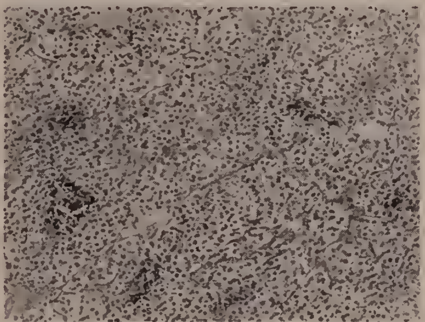

FIGURE 1. Tumor cells in dysgerminoma are strikingly uniform, with round, regular, vesicular nuclei and clear cytoplasm. They are present in nests within fibrous trabecula in classic histologic pattern. (hematoxylin and eosin stain, original magnification × 100)

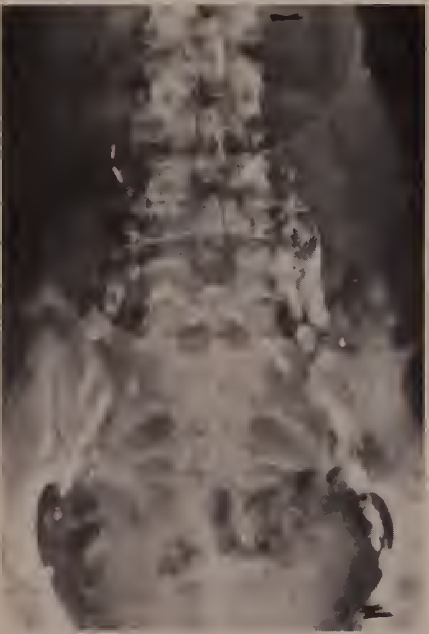

FIGURE 2. Postoperative lymphangiogram showing complete obstruction of dye above L-3 vertebra.

From the Brachytherapy Service, Department of Radiation Therapy, Memorial Sloan-Kettering Cancer Center, New York.

Address correspondence to Dr Nori, Assistant Attending Radiation Therapist, Brachytherapy Service, Department of Radiation Therapy, Memorial Sloan-Kettering Cancer Center, 1275 York Ave, New York, NY 10021.

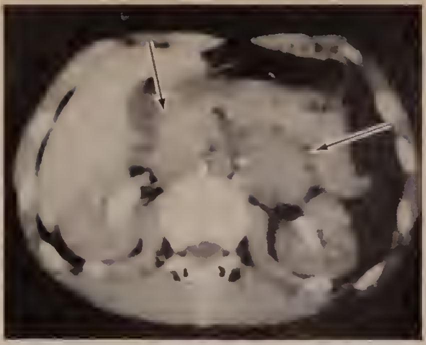

FIGURE 3. CT scan of abdomen prior to radiation therapy showing massive nodal disease at L-1–L-2 level (arrows), not visualized on the lymphangiogram.

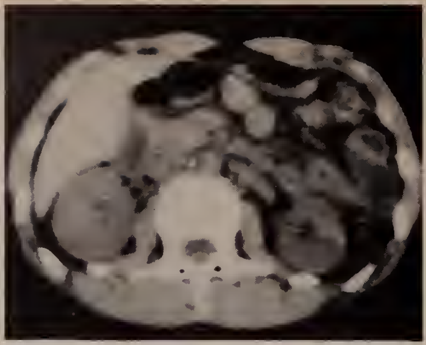

FIGURE 4. CT scan three months after treatment showing good response to radiation therapy.

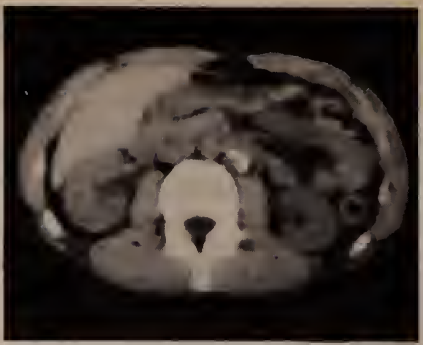

FIGURE 5. Normal CT scan at two-year follow up.

The patient was evaluated at three-month intervals, with repeated CT scans of the abdomen and pelvis at six-month intervals. The most recent CT scan (Fig 5) was within normal limits. Twenty-six months after completing radiation therapy, repeated laparotomy disclosed normal pelvic and para-aortic retroperitoneal spaces and normal biopsy specimens from all the areas previously involved with tumor.

DISCUSSION

Pure ovarian dysgerminomas are highly radiosensitive malignant neoplasms that occur largely in the first three decades of life, constituting about 2% of all ovarian malignant neoplasms. The prognosis for this treatable disease depends on several factors: the initial stage of the disorder at the time of diagnosis; histologic studies identifying a true "pure" dysgerminoma; and initial therapy appropriate for a lesion at a given stage. If these factors are all present, five-year survival rates for stage I and II are in the range of 90% to 100%[1]; even in more advanced stages, survival rates of 100% in a small series of patients have been reported.[2] Furthermore, 80% of recurrences have been reported to occur within the first two years and 75% within the first year[3]; therefore, accurate and frequent evaluation for disease status is particularly important in this time span.

Accurate means of follow-up evaluation takes on added importance in light of the reasonably high survival rate of patients with recurrences, if they are diagnosed early. Krepart et al[1] have reported a survival rate of seven of 10 patients with recurrent disease, and Freel and coworkers[4] report four of nine patients with recurrences as having no evidence of disease 18 months to 21 years after treatment.

De Palo et al[5] have reported on a series of 56 patients with pure dysgerminoma; 12 of 18 patients with stage III disease were diagnosed on the basis of positive para-aortic nodes alone, while four other patients with stage III disease had both para-aortic node and peritoneal involvement. In a small series, Marks et al[2] reported four of five patients as having stage III disease on the basis of para-aortic node involvement.

The importance of para-aortic nodes as a common site for spread of an ovarian dysgerminoma is well established, and the routine use of a preoperative or postoperative lymphangiogram, as described by various authors,[1,2,5,6] attests to the importance of evaluation of the para-aortic nodes in assessment of the extent of disease and subsequent treatment planning. As has been noted by Athey et al,[6] the major first-echelon lymph node drainage site for the ovaries is the para-aortic nodes; in patients with a variety of ovarian neoplasms, they found that of 33 abnormal lymphangiograms, 70% showed para-aortic node involvement.

The importance of continued, accurate post-treatment evaluation of the para-aortic nodes is illustrated in Krepart and coworkers' series,[1] in which five of 12 recurrences of ovarian dysgerminoma occurred in the para-aortic nodes.

In the patient we report on, information on para-aortic nodal size, provided by the CT scan of the abdomen and pelvis, was used to alter the treatment plan: whole-abdomen irradiation and pelvic, para-aortic, mediastinal, and supraclavicular irradiation were included. The lymphangiogram, which was not readable above the L-3 level, could not have provided this information. Furthermore, the initial CT scan was used as a base line to assess response to treatment and to determine the condition of the nodes at six-month intervals for more than two years after treatment.

In selected cases of pelvic malignant neoplasms, where retroperitoneal adenopathy may be so massive as to preclude accurate definition with a lymphangiogram and surgical exploration and clipping, the use of abdominal and pelvic CT scanning as an aid to defining the extent of nodal disease and in evaluating post-treatment nodal status should be considered.

Acknowledgment. Mrs Yvonne Lewis assisted in the preparation of the manuscript.

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Atypical radiographic appearance of a gastric eosinophilic granuloma

ALAN WECKSELL, MD, ELLEN KAHN, MD, MATTHEW J. MCKINLEY, MD,
RICHARD C. BRONZO, MD

Any large gastric mass has the potential of being malignant. When the mass is accompanied by diffuse, markedly thickened folds and diminished peristalsis, malignancy is the likely diagnosis. We describe a patient with a lobulated mass that was accompanied by secondary signs of malignancy which proved to be benign.

CASE REPORT

A 48-year-old woman who was receiving thioridazine hydrochloride for schizophrenia was admitted to North Shore University Hospital with recurrent nausea, vomiting, and sharp upper abdominal pain for four weeks' duration that was relieved by milk. A complete blood cell count three weeks before admission revealed hypochromic anemia, treated with ferrous sulfate. She denied having allergies. On examination, the patient was noted to be obese, cooperative, and in no distress. The upper abdomen was tender to palpation. Black stool was obtained from the rectum, and coffee-ground material was aspirated from the stomach.

Her white blood cell count on admission was 10,700/μL. The differential was 86% neutrophils, 9% lymphocytes, and no eosinophils. The hemoglobin value was 9.7 g/dL, and the hematocrit reading was 27%.

The patient received two units of packed red blood cells and was treated for presumed peptic ulcer disease with an antacid and cimetidine. On a series of single-contrast upper gastrointestinal roentgenograms, a large, well-marginated, slightly lobulated, and nonulcerated antral mass was identified. The sharp proximal and distal edges favored a submucosal origin; however, lobulation suggested a possible polypoid component. Because the folds throughout the stomach were markedly thickened, with minimal peristalsis seen on fluoroscopic analysis, a diffuse neoplastic process was considered (Fig 1).

Endoscopic examination revealed markedly erythematous gastric rugae and a large, centrally depressed ulcerated polypoid antral mass. Biopsy specimens from the mass yielded necrotic tissue, and no pathologic diagnosis was noted from the rugae.

A Bilroth II subtotal gastrectomy was performed. The antral mass was 4 cm in diameter, 1.5 cm thick, and had a yellow-tan cut surface. The surrounding rugae were edematous, measuring approximately 1 cm in thickness.

On microscopic examination the mass was composed of edematous, fibrous connective tissue, thin- and thick-walled vessels, many eosinophils, and a few mononuclear cells. The mass involved the submucosa and muscularis propria and, with associated ulceration, extended into the mucosa. The surrounding uninvolved gastric wall was characterized by marked submucosal edema (Fig 2). No dilated veins or lymphatics were seen. The pathologic diagnosis was gastric eosinophilic granuloma.

The patient's postoperative course was uneventful. A follow-up gastrointestinal roentgenographic series six months later revealed normal rugae in the gastric remnant (Fig 3).

DISCUSSION

The two most common names for the benign process described are eosinophilic granuloma and inflammatory fibroid polyp.

The tumor mass is usually sessile or, rarely, pedunculated. It is commonly located in the gastric antrum.[1] It has also been found in the gastric fundus, small bowel (usually lower ileum), colon, and esophagus.[2]

The gastrointestinal eosinophilic granuloma has no histologic relationship to the bone or lung lesion of the same name. The fibroblast is the basic cell in the gastrointestinal lesion. The histiocyte and reticulum cells are the basic cells in the bone and lung lesions. The eosinophils are evenly distributed in the gas-

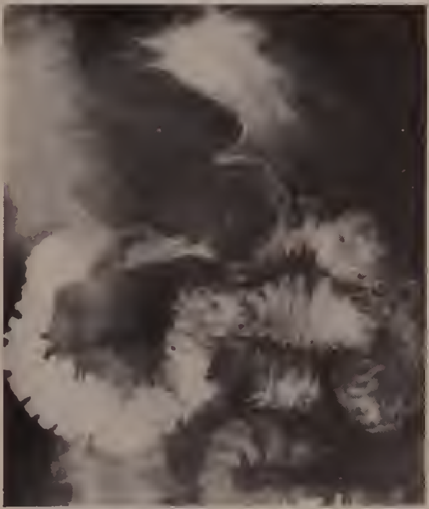

FIGURE 1. Single-contrast gastrointestinal roentgenograph reveals large, sharply marginated and slightly lobulated sessile antral mass. The rugae are thickened and gastric peristalsis is minimal.

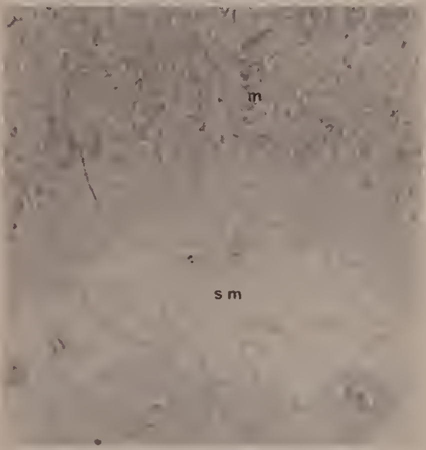

FIGURE 2. Section of stomach adjacent to granuloma shows widened edematous submucosa (sm) and normal gastric mucosa (m). (hematoxylin and eosin stain, original magnification × 50).

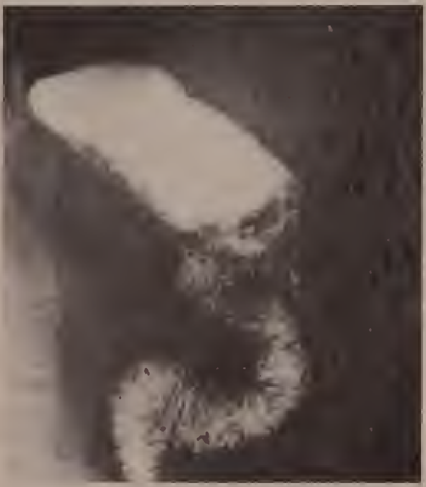

FIGURE 3. Rugal folds in postoperative gastric remnant are normal.

From the Departments of Radiology (Dr Wecksell), Laboratories (Dr Kahn), and Medicine (Drs McKinley and Bronzo), North Shore University Hospital, Cornell University Medical College, New York.

Address correspondence to Dr Wecksell, Department of Radiology, North Shore University Hospital, 300 Community Dr, Manhasset, NY 11030.

trointestinal lesion and haphazardly distributed in the bone and lung lesions.[3]

The eosinophilic granuloma can easily be differentiated from eosinophilic gastritis and gastroenteritis. The granuloma is a solitary mass, unrelated to an allergic history, unaccompanied by eosinophilia, and curable with surgical resection. Gastritis or gastroenteritis is a diffuse disease process, often seen in an allergic patient, accompanied by eosinophilia, and controlled with steroid therapy. A patient with a gastric eosinophilic granuloma usually exhibits melena due to ulceration, or gradually increasing abdominal pain due to obstruction. If the tumor mass is located in the gastric antrum, it may prolapse through the pyloric channel and markedly enhance the obstructive symptoms.

Roentgenographic gastrointestinal studies usually reveal a sessile polypoid gastric mass. Unlike this case, the surrounding gastric rugae would be normal. If the mass is large, regardless of the adjacent mucosa, one would be most concerned about adenocarcinoma or lymphoma. If sharp acute angles are discernible at the edges, with or without ulceration, one would consider gastric leiomyoma or leiomyosarcoma. If several small asymptomatic intragastric filling defects are identified, benign gastric polyps would be more likely. A rare carcinoid tumor could appear as a large intramural or polypoid mass that may ulcerate.[4] Endoscopic examination would reveal a granular erythematous mass usually found in the gastric antrum.[5]

The gastric eosinophilic granuloma seen in this patient exhibited important secondary roentgenographic and endoscopic signs of malignancy. Although no evidence of venous or lymphatic engorgement was identified, the severely edematous gastric rugae are believed to have resulted from marked compression by the tumor mass against adjacent tissue.

Acknowledgment. Irving Wecksell, MD, Robin Stein, and Tina Velsor aided in the preparation of this article.

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Repair of post-traumatic complete bronchial stricture

PAUL R. G. CUNNINGHAM, MD, PAUL A. KIRSCHNER, MD

Disturbance of the ventilation/perfusion (V/Q) relationship, known as reflex hypoxic pulmonary vasoconstriction, and its restoration to normal with surgery is described in a patient with complete bronchial stricture following trauma. Radionuclide V/Q lung scans are a simple, non-invasive method for demonstrating pulmonary vasoconstriction.

CASE REPORT

A 28-year-old man sustained a crushing injury to the chest when he was pinned between two trucks. He lost consciousness for about five minutes, and then had difficulty in breathing associated with wheezing and slight hemoptysis. An initial roentgenogram showed mediastinal emphysema including the "V-sign" of Naclerio.[1] There were no fractured ribs. He spent two days in an intensive care unit in another hospital.

Twelve days later shortness of breath and wheezing continued, and a chest film showed diminished vascularity in the left lung field. Eighteen days after the injury he awoke with marked dyspnea, and the wheezing had ceased. A chest film now showed atelectasis of the entire left lung. Tomography revealed complete occlusion of the left main bronchus; this was confirmed by bronchoscopy. Arterial oxygen tension was 48 torr on room air, rising to 84 torr on FiO_2 of 0.4.

The patient was transferred to the Mount Sinai Hospital in severe respiratory distress. He had a temperature of 101.4°F; pulse rate, 120/min; and blood pressure, 140/100 mm Hg. The trachea was deviated to the left, and breath sounds were absent on that side. Laboratory data were hemoglobin, 14.8 g/dL; hematocrit, 46.8%; leukocytes, 23,400/mm^3. Arterial blood gases had a Po_2, 68.7 torr; Pco_2, 32.8 torr; and pH, 7.49 on room air. On FiO_2 0.4, Po_2 fell to 60.6 torr, Pco_2 rose to 43.6 torr, and pH fell to 7.43.

V/Q lung scans showed absent uptake in the left lung (Fig 1). Pulmonary angiography revealed bilateral patency of the vascular bed, but there was marked delay in perfusion of the left lung associated with disappearance of the finer arterial radicles.

Four days after the onset of complete bronchial occlusion, arterial blood gas levels had returned to almost normal levels: Po_2, 79.4 torr; Pco_2, 39.5 torr; and pH, 7.47 on room air. Surgery was performed the following day, 23 days after the injury and five days after the appearance of complete bronchial obstruction. Rigid bronchoscopy confirmed complete stenosis of the left main bronchus at its midpoint. A thoracotomy of the left side of the chest was performed using a right endobronchial double-lumen anesthesia tube. The left lung was completely atelectatic. There was an hourglass constriction of the left main bronchus. The pulmonary vessels were patent. The segment of occluded bronchus, measuring 1.5 cm in length, was resected.

A pale creamy fluid flowed from the distal bronchial lumen. A culture of the fluid grew no organisms. After irrigating the bronchial tree of the left lung with normal saline solution, an end-to-end bronchial anastomosis was constructed with a single layer of 5-0 Ethibond® sutures and was covered with pleura. The left lung became fully inflated immediately. Bronchoscopy after thoracotomy confirmed a patent anastomosis.

The patient remained afebrile after surgery. The left lung showed immediate and sustained expansion, and a fluffy infiltrate cleared rapidly. Arterial blood gas levels with an endotracheal tube in place were PO_2, 109 torr; Pco_2, 42 torr; and pH, 7.42. Ten days after surgery these measurements were Po_2, 83.4 torr; Pco_2, 38.1 torr; and pH, 7.42 on room air. V/Q scans on the eighth day after surgery were unremarkable (Figs 2, 3). To-

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From the Section of General Thoracic Surgery, Division of Cardiothoracic Surgery (Dr Kirschner), Mount Sinai Medical Center, and the Department of Surgery, (Dr Cunningham), Joint Diseases North General Hospital, New York.

Address correspondence to Dr Kirschner, 2 East 92 St, New York, NY 10128.

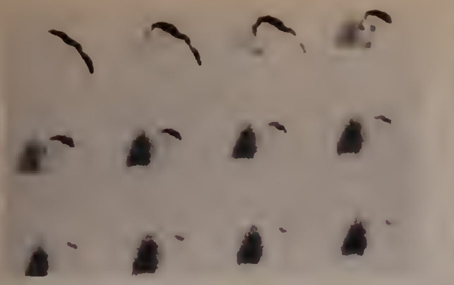

FIGURE 1. Preoperative perfusion scan. Note absent perfusion of left lung.

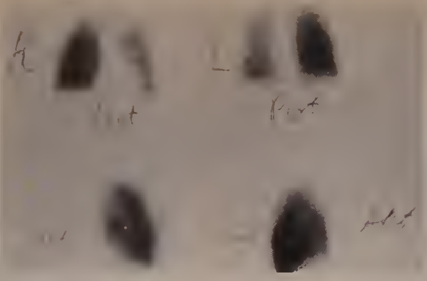

FIGURE 2. Postoperative perfusion scan. The left lung is now perfused.

mography showed a patent left main bronchial lumen.

Eight months after the operation a chest roentgenogram showed bilateral aerated lung fields. The patient was able to swim the length of an Olympic-size swimming pool underwater. Fifteen months after surgery, his vital capacity was 3.7 L; forced expiratory volume, 3.25 L; and forced expiratory volume/forced vital capacity ratio, 88%. The maximal respiratory flow rate was 350 L/min.

DISCUSSION

The first successful resection of a posttraumatic stricture of the left main bronchus was reported by Griffith in 1948.[2] Since then numerous such procedures have been accomplished with restoration of normal pulmonary function up to 15 years after injury.[3-5]

Considerable information is now available concerning the regional interrelationship of pulmonary ventilation and blood flow.[6,7] Hypoxia due to an obstructed bronchus activates a pulmonary arterial vasoconstrictor reflex in that area. This is reversed by restoration of the bronchial lumen and correction of hypoxia.[8,9] This phenomenon can be demonstrated with radionuclide V/Q scanning[6,7] and pulmonary angiography.[9] Both methods were used on this patient.

The reflex can be abolished by volatile anesthetic agents as, for example, in the use of one-lung anesthesia.[10] Intravenous anesthetic agents such as ketamine do not appear to affect this reflex.[11]

This vasomotor phenomenon has been seen in a number of clinical situations, including neoplastic bronchial obstruction (benign or malignant),[12,13] stricture (traumatic or inflammatory),[12] (Fig 4), presence of a foreign body,[14,15] one-lung anesthesia,[10,11] or a malpositioned endotracheal tube.[16] Serial V/Q nuclear scans can be used to diagnose and document reflex hypoxic pulmonary vasoconstriction and its restoration to normal after surgical repair. Pulmonary angiography can be dispensed with in most cases, unless specific information regarding the patency of the vessels is required. In this regard, nonperfusion of the affected lung when a tumor is present should not necessarily imply that there has been neoplastic vascular involvement. Such information is essential in determining whether or not the lesion can be resected.

There appears to be almost no time limit to the restoration of pulmonary function by resection of the stricture and bronchial anastomosis. Successful results have been obtained up to 15 years after an injury.

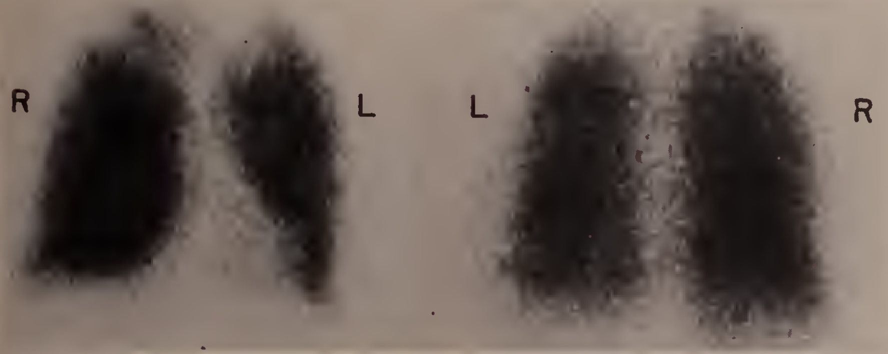

FIGURE 3. Postoperative ventilation scan: left, anterior view; right, posterior view. The left lung is now ventilated.

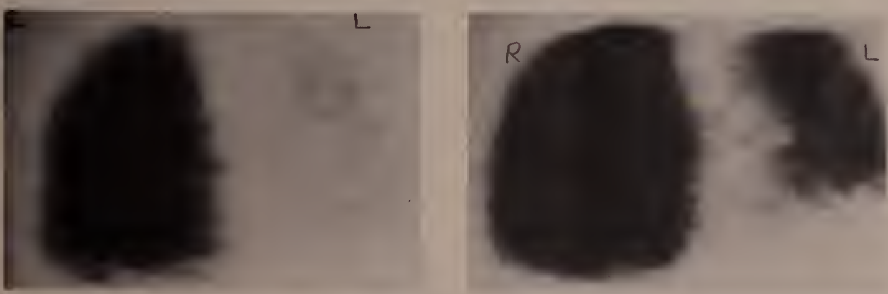

FIGURE 4. Left, perfusion scan in patient with granulation tissue obstructing left main bronchus; Right, perfusion scan after bronchoscopic removal of granulation tissue.

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Hypoxia: can brain cells recover?

The belief that nerve cells in the brain cannot survive more than about five minutes of ischemia or severe hypoxia is being challenged.

Evidence collected during the past 10 years has led researchers to develop a new hypothesis: neurons and synaptic function can survive 5, 10, and even 15 minutes of ischemia. However, when the general circulation is restored, the cerebral microcirculation cannot provide sufficient amounts of oxygen or purge the metabolites accumulated during the ischemia. Capillaries and small arterioles are so affected by the ischemia that they do not regain normal flow, and the brain cells ultimately die because of prolonged lack of oxygen. Some reports have suggested that nerve cells can live up to an hour and can recover metabolic and synaptic function if they receive adequate blood supply.

Such ideas would have been heresy prior to the 1960s, when studies uncovered several paradoxes that raised doubts about the vulnerability of nerve cells. Using in vitro techniques, investigators learned that central nerve cells, retinal cells, and optic nerve cells were able to withstand long periods of anoxia. When oxygen was restored the cells resumed a normal level of metabolic activity. The ultra-thin layer of cells were bathed in generous amounts of oxygen and nutrients that would not be available in the in vivo situation if the microcirculation were disrupted. In other experiments, brief periods of cerebral ischemia caused widespread deleterious changes in the microvasculature that were linked with death or poor recovery of the animals.

The evidence was minimal and circumstantial, but researchers began to question whether impaired recirculation could be the primary reason for the death or incomplete recovery in humans and animals who suffer brief periods of global ischemia.

NO-REFLOW REVISITED

In 1968 Dr Adelbert Ames III and his colleagues from the Harvard Medical School reported a "no-reflow phenomenon," which they discovered in the ischemic brain (*Am J Pathol* 1968; 52:437–453). They concluded that the clogged microvessels seen throughout the brain were due to a decreased caliber of the lumen and increased blood viscosity, noting that the no-reflow state of the microcirculation could be the first irreversible change seen in ischemia. This study lent strong support to a suggestion by Dr W. A. Neely and Dr J. R. Youmans in 1963 that the damaged vessels may contribute to ischemic injury (*JAMA* 1963; 183:1085–1087).

If the problem resided with poor restitution of the microcirculation rather than immediate cell death or irreversible changes in cell function, then the solution would require a means of restoring capillary flow.

The possibility remained that brain cells simply could not tolerate brief periods of hypoxia. And, even if they could, restoration of metabolism, oxygen consumption, and electrophysiologic signals was no assurance that synaptic integrity and higher functions were preserved intact. Nonetheless, with the hope that correction of perfusion defects would lead to recovery, a few laboratories around the world began to investigate the reason for the shutdown of the microvasculature after ischemia.

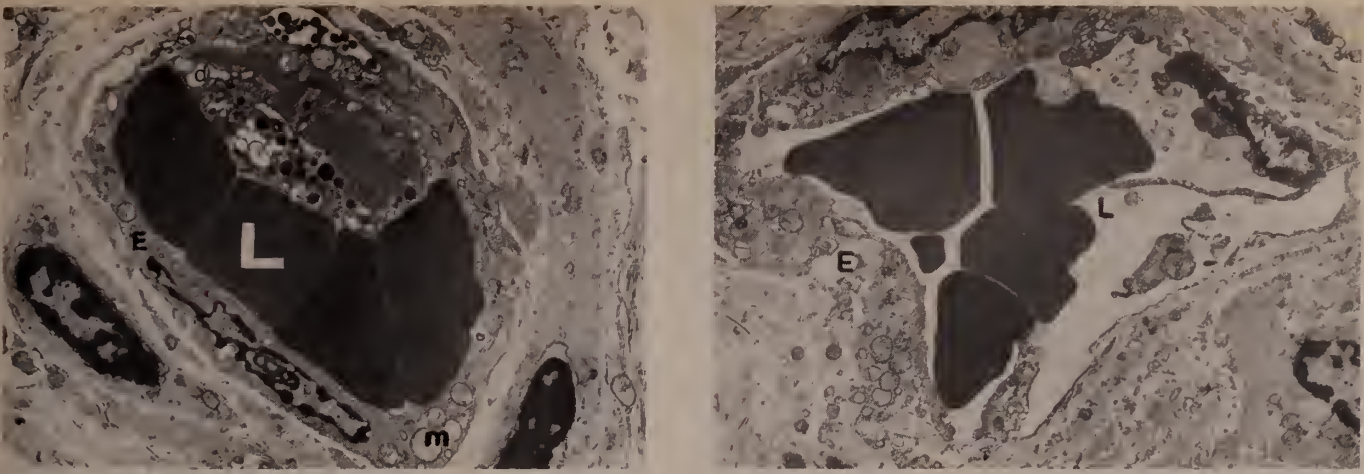
Several theories began to emerge: swelling of capillary cells and perivascular glial cells as a cause of compression of the lumen; blood aggregates in arterioles and microemboli; a large increase in potassium concentration in the extracellular space, causing a contraction of vascular smooth muscle in arterioles or arteries, or both; neurogenic spasm of arterial smooth muscle; swollen erythrocytes and increased blood viscosity; disseminated intravascular coagulation ("consumption coagulopathy") which impairs postischemic brain, liver, kidney, and lung function due to microemboli; a mysterious reaction at the tissue-blood interface that reduces recirculation by an unspecified mechanism (the reaction can be eliminated and postischemic flow improved by shunting the blood through glass wool prior to the ischemic insult); and impaired reactivity to carbon dioxide, which largely controls local blood flow in healthy tissue.

One group presented convincing evidence of capillary blockage by swollen "blebs" that appeared to have been sloughed from vascular endothelium. However, subsequent studies proved that the blebs were postmortem artifacts of the tissue-fixing procedure.

CLUES IN LOW-REFLOW

While Ames and coworkers implicated a no-reflow phenomenon, other laboratories found a low-reflow phase. The period of ischemia was followed by a reactive hyperemia that caused local cerebral blood flow to increase by as much as 300%, and rarely up to 600%. The hyperemia, presumably caused by a local accumulation of lactic acid and carbon dioxide, persisted for about 30 minutes and was followed by a sharp decrease in blood flow to about 60% of normal levels. Although the electroencephalogram showed signs of recovery during the hyperemic phase, it decreased abruptly during the onset of impaired flow, indicating that good blood flow was associated with cerebral recovery.

One team of investigators detected subnormal local flows in non-specific areas of the cortex during general hyperemia. This implied that at least two different mechanisms were affecting blood flow. It is likely that a number of



Photomicrographs of skin flap sections (which are more resistant to ischemia than brain tissue) demonstrating the no-reflow phenomenon. Left, a lumen (L) which has become irreversibly engorged with blood after 12 hours of ischemia. The endothelium (E) is intact but shows some ischemic damage, and the mitochondrion (M) have degenerated. Right, a microvessel which has almost completely disintegrated after 12 hours of ischemia. The lumen (L) has become impacted with distorted blood cells, and the endothelium (E) has been totally disrupted.

interrelated factors are responsible for no-reflow or low-reflow. This may explain why investigators have had such a difficult task in perfecting techniques for resuscitating the ischemic brain. Whether investigators have found no-reflow or hyperemia followed by low-reflow, evidence continued to support the suspicion that disruption of the circulation is the prime reason for a poor prognosis.

Dr Konstantin-Alexander Hossmann has been one of the leaders in this field of research since the publication of his first paper on ischemia in 1973. He and his colleagues at the Max Planck Institute for Neurological Research in Köln, West Germany have focused their studies on the factors that contribute to the recovery of metabolism and blood flow after prolonged ischemia. "I became interested in the possibility that nerve cells can withstand long periods of ischemia while studying ischemic damage of the blood-brain barrier," Hossmann told the *Journal*. "We were studying the critical length of ischemia that would cause a breakdown of the blood-brain barrier to blood proteins. It turned out that after ischemia of 30 minutes—and even after 60 minutes—the blood-brain barrier did not break down. And evoked potentials [from the cortex] returned when flow-promoting procedures were used to improve postischemic recirculation."

SELECTIVE VULNERABILITY

Understandably, these findings aroused tremendous interest among clinicians and medical researchers around the world. Although the circulation has been implicated in the failure of the central nervous system to reanimate after ischemia, convincing evidence still supports the concept of "selective vulnerability"of certain areas of the brain. Some investigators claim that virtually all areas of the brain may have the capacity to survive relatively brief periods of ischemia, but others hold that specific areas are selectively vulnerable even if postischemic blood flow is adequate. "Most authors agree that some structures—such as Purkinje cells, the striatum, and in particular, sections of the hippocampus—are irreversibly damaged by ischemia as brief as five minutes. This happens even in the absence of any disturbance to the microcirculation," Hossmann said. "In contrast, my research indicates that revival of the rest of the brain seems to depend mainly on the quality of the postischemic reperfusion."

Restoring oxygen in vitro to a thin slice of tissue is a simple matter, but supplying adequate oxygen to intact tissues is a problem not yet solved. According to the principles of fluid mechanics, the ways of promoting flow are to increase pressure, decrease resistance to flow, or decrease viscosity.

An increase in pressure has been achieved using vasopressor drugs, but cerebral edema often results. The edema is apparently due to imbalances between intracellular and extracellular ionic homeostasis, increased intravascular filtration pressure, and mechanical disruption of "tight junctions" between capillary cells. Treatment of the edema using hyperosmolar solutions, with a consequent improvement in local flow, has been equivocal. Thus, while depressed flow can be elevated with a concomitant improvement in cerebral function, the improvement is transient.

Use of vasoactive drugs to decrease vascular resistance can incite profound dilation of normal vessels. However, following ischemia, these drugs do not substantially improve the recovery of local flow or electrophysiologic function. The vessels' sensitivity to vasodilators may be reduced, or, in regions with severely impaired reflow, the substance simply may not be reaching the microvessels. Additionally, vasodilators may promote a "steal" syndrome by shunting flow to one region at the expense of oxygen-starved tissues.

Reduction of blood viscosity by isotonic dilution has resulted in elevated local blood flow. Paradoxically, the improved flow was negated due to the decrease in the oxygen-carrying capacity of the blood. Using anticoagulants and other blood thinners, investigators have reported conflicting results, and no one has demonstrated an extraordinary improvement solely attributable to a decrease in blood viscosity.

FRACTIONAL REANIMATION

In brief, investigators are still searching for a safe technique that can fully—or at least adequately—restore the microcirculation following ischemia. Hossmann predicts that such research will focus on two areas: "First is the elucidation of the phenomenon of selective vulnerability that is seen in certain structures within the brain. I anticipate that this will be clarified in the near future. Second is the reanimation of the central nervous system after prolonged ischemia. Researchers still need to show that, following ischemia, the brain not only recovers biochemical and electrophysiological functions but also resumes its integrative neuronal functions. I feel that this proof can be provided in the near future."

"Once this has been established," Hossmann notes, "investigators must concentrate efforts on reanimating the brain after prolonged cardiac arrest rather than simply an isolated cerebrocirculatory arrest." (Such research has been reported, but results have been poor or inconclusive. Because of the numerous drugs used to support a failing heart, the extent of recovery of the brain and its capacity to recover following cardiac arrest are uncertain.) "The main problem will be to protect the brain from low blood flow during the period of cardiac rususcitation. This could be done by what we call 'fractional reanimation'—that is, by delaying reperfusion of the brain until full cardiac function has been resumed. Or reperfusion of the whole body could be started using extracorporeal circulation."

What is the clinical forecast for resuscitation of a brain that would have been considered hopelessly damaged only several years ago? "Either of these procedures [fractional reanimation or extracorporeal circulation] could possibly be combined with induced hypothermia, but a considerable amount of experimentation awaits us before these methods are perfected and applicable to a clinical situation," according to Hossmann. Therefore, I do not believe such methods will be introduced for use on humans in the near future."

The topic of brain cell vulnerability and hypoxia are noteworthy for controversy and conflicting evidence: hypertension promotes edema—hypertension does not aggravate edema and helps to resolve it; vasodilators are beneficial—vasodilators are useless or even detrimental; vasospasm is responsible for low-reflow—thrombi and perivascular swelling are the villains.

Because of these contradictory results, no one has been able to propose a unified theory that accounts for the mechanisms of brain damage and resuscitation following ischemia. Despite this failing and amid the conflicting reports, investigators still agree that central nerve cells are not always fatally injured by relatively brief periods of ischemia. Hope does exist.

This hypothesis will receive its ultimate test when researchers devise a regimen to fully reestablish the microcirculation.

Calvin Miller, PhD

Calvin Miller is a medical and science writer based in Taree, New South Wales.

FROM THE LIBRARY

A LAYMAN'S REVIEW

A great number of medical clippings from the daily press were recently put into my hands, and my lay opinion was asked as to their popular interest and value. The general purpose of these articles is not only to arouse the interest of the people, but also to educate them; not only to advertise medical activities throughout the State, but also to arouse a sympathetic interest in these activities, which will lead to a public benefit.

These clippings covering the month of July seemed to fail utterly in their main purpose—that of arousing interest. They seemed to be successful only in so far as they filled up newspaper space. A very large percentage failed even to interest . . . .

The article which interested me most related to scabies. It gave the history, symptoms, and cure of the disease in a simple, direct way. It had the professional tone of authority, and led me to feel that I was learning something which might at some time serve a purpose. Now, we have never had scabies, and do not know of any one that ever had scabies. In fact we are not sure we ever heard of it before, and so the interest we took in the article could hardly have been a personal one. The interest was due to the nature of the article. To many the newspaper is a primary source of certain kinds of information, and real information is usually appreciated. Health is a subject in which the general public takes a real interest, because to most of us it represents a goal not quite attained. The people generally are able to take a far more intelligent interest in things medical than is credited to them by those who have had a professional training, if one can judge at all by these sample clippings. We believe that the people would understand and appreciate a greater number of items of a scientific nature.

Professional education through the press undoubtedly has a large field of opportunity, but its aims so hopefully set forth can only be realized when more professional time and interest is given to the press articles by those physicians who are able to write them.

ALBERT LEE KLAER, AB
(*NY State J Med* 1925; 25:917–918)

ABORTION AND THE POLITICS OF MOTHERHOOD

By Kristin Luker. 324 pp, illustrated. Berkeley, University of California Press, 1984. $14.95 (hardcover)

This book is a timely, historical accounting and analysis of the social attitudes that underlie the pro-choice and pro-life positions in the debate on abortion. The author is an associate professor of sociology at the University of California, San Diego. Through comprehensive interviews with 200 women known for their activism on the abortion issue, Luker draws an in-depth picture of the moral, social, and economic climate propelling this struggle forward.

The book offers a historical perspective in the first three chapters and a full discussion of abortion reform and its link to the women's movement in chapters four and five. This is followed by a thorough description of the polarization of the two opposing forces in chapters six and seven, and a final chapter which offers an assessment of the current cultural and political significance inherent in the abortion issue.

The historical overview provides the reader with a much greater appreciation of how recent developments have shaped what in earlier times was a private issue, later a silent one, and now a heated political controversy threatening the traditional separation of church and state. Until the mid-19th century, abortions took place in the privacy of homes and were not subject to public discussion or action. Luker attributes the anti-abortion laws of the late 19th century to a number of factors, the most interesting of which was the role of the "elite" or "regular" physician. Luker considers that it was the planned, collective strategy of these physicians to invest themselves with the power to provide both the technology and moral responsibility capable of rendering control over the decision-making process of allowing or prohibiting abortion. As abortion decisions became medical issues for the first time, these physicians had in effect separated themselves from "lesser" physicians and healers and succeeded in upgrading their professional and moral status. For the next century, decisions regarding abortion rested with physicians.

These decisions as to whether to permit an abortion rested on a variety of factors ranging from what constituted a threat to a mother's life to individual interpretations based on personal and professional viewpoints.

Only as technology moved medical practice into hospital settings, and the risks to the mother's life became rare, was the decision-making responsibility of the physician questioned. This resulted in a split between physicians' values and acceptable professional actions. Some physicians sought assistance from the judicial system in clarifying the risks they were taking and the latitude permitted them in their decision-making role. The woman's movement joined forces with this group, reinterpreting the issue as one of women's rights and choices. The Right to Life Movement also began to mobilize its energies. The women's movement and right to life interests have evolved into two very different constituencies, whose experiences, resources, and views reflect a chasm of enormous and seemingly unalterable proportions.

Luker develops a profile of the women in each group. One's beliefs in regard to the meaning of life and death, parenthood, sexuality, morality, and the role of women are an intrinsic part of one's position in this struggle. She describes the pro-choice activist as more likely to have been married at age 22 or older, and to be in her 40s with one or two children, a college graduate, married to a professional, and employed herself. The pro-life activist is more likely to have married at age 17, have three or more children, have a father who graduated from high school, not work outside the home, and be married to a small business man or a lower income white collar worker.

These differences in social background lead to opposing views on the definition of the rights of embryos, the rights and protection due mothers, and women's rights to have equal access to the job market.

Luker concludes this comprehensive assessment of one of the most heated and controversial social issues of our time with a projection on the possible outcomes of this debate. She is a thorough, insightful, and disciplined scholar. The book is of value to those interested in pursuing this subject in its historical, political, and sociological context. Although there is an over-elaboration of information in some sections, the material permits the reader to become well informed about a subject pivotal to how this society deals with religious and cultural pluralism. It also challenges the reader to pursue a more analytic examination of the prevailing social roles and values that effect our lives and decisions.

ZELDA FOSTER, MSW
Brooklyn Veterans Administration
Medical Center
New York City 11209

ATLAS OF HUMAN CROSS-SECTIONAL ANATOMY

By Donald R. Cahill and Matthew J. Orlando. 139 pp, illustrated. Philadelphia, Lea & Febiger, 1984. $29.50 (hardcover)

With the advent of computed tomography, ultrasound and nuclear magnetic resonance (NMR) visualization of sections of the internal human body, it has become increasingly important to have a good understanding of cross-sectional anatomy. The standard anatomical atlases and textbooks have responded to this need in a limited manner, but comprehensive atlases of human cross-sectional anatomy such as the one compiled by Cahill and Orlando are clearly useful reference sources.

The authors are well qualified to undertake the task of compiling this atlas, since Cahill is an experienced and highly qualified teacher of anatomy, and Orlando is a clinician who has been able to draw particular attention to structures that are of importance in the training of future radiologists, internists and surgeons.

The basic plan of the book is excellent. Frozen sections of the thorax, abdomen and pelvis cut at approximately one inch intervals are presented. The superior and inferior surface of each section is photographed, usually while still frozen, so that anatomical relationships are well preserved. Photographs of opposing sections are displayed on opposing pages of the atlas, and only the major structures are labeled. A detailed drawing of each section is also presented on each page with about four times as many structures labeled. This amount of detail was made possible by dissecting each section after thawing. Also on each double page is an anterior view line drawing of the skeleton of the trunk of the body showing the position of each section with the specific sections pictured on those two pages indicated with a darker line. The male and female pelvis are each shown in a separate series of photographs and drawings. There are also two series of sections through the head: one series is at an angle of 20° from the orbitomeatal plane (7 sections) and the other series is in the orbitomeatal plane (14 sections).

The quality of the photography in this atlas is quite good. Many structures, including vessels, can be readily identified. The drawings by Cahill are excellent and show detail much more clearly than in competing atlases. A great deal of care has gone into the identification of structures so that this reviewer has not found any obvious errors in labelling.

One disadvantage of the basic design of this atlas is that it was necessary to reduce each photograph to about one-fourth to one-third its actual size. The drawings of individual sections are somewhat larger.

This style of atlas will be particularly useful to both anatomists and to those clinicians using computer tomography, ultrasound, and NMR pictures. For this reason it is likely that atlases which allow close approximation of cross-sectioned cadaver photographs with photographs utilizing one or more of these diagnostic tools may have broader utility.

In summary, the authors have succeeded in providing an excellent sourcebook for the anatomist to learn cross-sectional morphology, and it will also serve to help clinicians who are interested in developing expertise in the interpretation of cross-sectional imaging.

GEORGE TALBERT, PHD
State University of New York
Downstate Medical Center
New York, NY 11203

ENDOCRINE DIAGNOSIS: CLINICAL AND LABORATORY APPROACH

Edited by William F. Streck, MD and Dean H. Lockwood, MD. 330 pp, illustrated. Boston, Little, Brown & Co, 1983. $22.50 (hardcover)

This handbook of clinical and laboratory approaches to endocrine diagnosis is a welcome addition to the endocrine reference literature. Seventeen chapters are skillfully authored by 14 contributors. In each chapter a section on clinical manifestations (sometimes preceded by several paragraphs of general exposition) is followed by a description of appropriate diagnostic tests. Hormone assays are described, along with normal ranges for both random samples and provocative testing. Potential pitfalls are enumerated, including reasons for false positive and false negative tests. The last and most informative section of each chapter is the discussion, in which differential diagnoses are outlined and laboratory techniques are ranked according to their relative effectiveness, taking cost into account. Algorithms and flow charts abound throughout the book, providing graphic representation of the endocrine diagnostic process. Each chapter includes a comprehensive reference list of timely value to both practitioners and teachers.

The coherence and crispness of the individual chapters testify to the editorial skills of Streck and Lockwood. All unnecessary verbiage has been eliminated, making each contribution a storehouse of medical facts without undue theorizing or speculation. Although individual author bias is evident in some chapters, for the most part the flow sheets and recommendations are in agreement with the current thinking of endocrinologists.

In short, this is a handy volume that will be consulted frequently as specific clinical situations present themselves. It fills the gap between endocrine texts and superficial "how to" books, and should be of value to both physicians in general practice and specialists.

MARVIN M. LIPMAN, MD
Westchester County Medical Center
Valhalla, NY 10595

PATIENT-CENTERED AUDIT

By Christine G. Kruse, RN, BSN, Silvia A. Maher, RN, MS, Caroline Watson, ART. 70 pp, illustrated. St Louis, Warren H. Green, Inc, 1983. $14.50 (softcover).

In an all-encompassing statement in the Introduction the authors state that this book "pulls together all of the ideas, ideals and experiences so far in the multidisciplinary audit venture. Not only is there information on the basis of audit, but also the Accountability issue, history, and why we feel multidisciplinary is the *best* way to initiate an audit." Despite the breadth and depth of that statement, the authors take only 70 pages to present their case.

There can be no doubt that health care professionals should know a great deal of the material presented in this book. There is also no doubt that many physicians are not aware of the basic workings of multidisciplinary audits and should know more about the procedures. However, I doubt if many physicians will read this book. Two of the authors are registered nurses and the other is a medical records expert, and those professional groups appear to be the intended audience. Perhaps additional allied health professionals can be included in the intended audience.

This book details the steps in setting up a multidisciplinary audit system, with charts and easy-to-follow listings of people involved and the advantages of the multidisciplinary system over the department and/or parallel audit systems. There are 14 chapters in the book, and some are a single page long. A chapter on criteria points toward mechanisms for achieving objectivity in measurements. Another chapter discusses parameters for choosing topics and objectives. In the history chapter the authors describe the functions of 12 health professionals and the background of the Joint Commission on the Accreditation of Hospitals. These descriptions are modest and could not be called detailed job analyses. While there is an appendix containing definitions, there is no index and no listing of acronyms, of which there are considerable mentioned in the book.

Since the book was published in 1983, it is difficult to understand how one can discuss Professional Standard Review Organizations (PSROs) without noting that the current prognosis for PSROs is unstable to say the least. Federal Government initiatives to limit regulations and to diminish PSROs, Health Systems Agencies (HSAs) and other regulatory activities must have an impact on audit activities. In addition, there was no mention of Diagnosis Related Groups

(DRGs) and that reimbursement mechanism's impact on patient-care audits.

In addition, there is a "preachy" tone used toward the reader. Statements such as "professionals are social monopolies," "no longer will 'reflex practice' be acceptable," and "this is not the time for throwing punches and undermining" tend to grate on this reader as unnecessary platitudes.

There are important points to be made in this book, such as the use of a patient focus for the audit and the utilization of an outcome/process methodology for measurements. There are numerous charts, forms, diagrams and other visual aids that are useful to those concerned with patient-centered audits.

Nevertheless this book requires too much effort to extract the good from the inaccurate or unnecessary material. The authors cannot claim to have met the objective stated at the beginning of this review.

ALLEN D. SPIEGEL, PHD, MPH
State University of New York
Downstate Medical Center
New York City 11203

MARRIED TO THEIR CAREERS: CAREER & FAMILY DILEMMAS IN DOCTORS' LIVES

By Lane A. Gerber. 190 pp. New York, Tavistock Publications, 1983. $19.95 (hardcover), $9.95 (softcover)

In this book the author explores the difficulties for physicians in balancing the demands of family and medicine. Such a project is not novel, but the author refrains from citing the dismal statistics on divorce rates, substance abuse and suicides. Instead, he analyzes case histories of students, interns, residents, and their families in order to discern the roots of physicians' social problems. The result is an excellent evaluation of the career/family conflict which not only addresses the problems, but suggests some solutions as well.

Dr Gerber, a clinical psychologist and dean of student affairs at the University of Washington School of Medicine, spent several years recording the experiences of students and physicians throughout their training. In addition, the families of the physicians and students were interviewed, as were faculty members and colleagues. From this large pool of data, the author selected a few representative cases of both good and bad career/family situations.

After presenting the cases, he hypothesizes about the factors that determine a successful career/family relationship. In particular, the concepts of time, work, and caring are applied to subsequent case presentations. The result is not a guaranteed recipe for success, but rather a mirror in which one can reflect upon his or her personal situation and attitudes.

Gerber's presentation of his "data" provides the reader with clear-cut examples. The case history format makes the book enjoyable to read. Although the text is not very long, the amount of practical information presented is tremendous.

Everyone has to cope with career/family conflicts in one form or another. The energy and time demands of caring for patients often leave little time for family and home. As a group committed to caring for others, physicians must decide when their personal and families' needs are more important. In facing this dilemma, medical students and physicians should appreciate all the helpful advice and experience they can find. Therefore, this book is highly recommended reading. It is hoped that this is the first in a series of books that will help answer the question "How do you combine work and family life?"

GREGG S. MEYER
Second Year Medical Student
Albany Medical College
Albany, NY 12208

SURVIVING YOUR HEART ATTACK. THE DUKE UNIVERSITY COMPLETE HEART TREATMENT PROGRAM

By James V. Warren, MD and Genell J. Subak-Sharpe. 202 pp. Garden City, Doubleday & Co, Inc, 1984. $13.95 (hardcover)

The rehabilitation of patients recovering from a myocardial infarction poses special challenges to physicians. The Duke University Complete Heart Treatment Program (DUPAC), founded by Andrew G. Wallace, MD, is a comprehensive and reasonable approach to this problem that enjoys proven success.

Although the DUPAC program is well known to many physicians, it is known to only a small proportion of Americans. This extremely well written book should go a long way in bringing the philosophy and guidelines of DUPAC to that segment of the population that can most benefit from them. Written for the lay public by James V. Warren, MD, a leading cardiologist and former president of the American Heart Association, and Genell Subak-Sharpe, an experienced medical writer, it provides both a detailed overview of the DUPAC program and general coverage of issues pertinent to the prevention of coronary artery disease.

The first third of the book consists of six chapters that are essentially a preamble to the indepth discussion of the DUPAC program that follows. These chapters discuss the anatomy and physiology of the heart and the role of various risk factors such as hypertension, cigarette smoking, diet, stress, exercise, obesity, diabetes, and personality type in the development of coronary artery disease. Age, sex, and genetic factors are also discussed. This is followed by a clear and concise discussion of the various types of heart disease and by three anecdotal case histories that illustrate the effects of risk factors as well as successful recovery following myocardial infarction.

The DUPAC program, which hinges on exercise conditioning and diet is described in great detail. This is followed by a chapter "Stress, Personality and Heart Disease" that clearly describes Type A personality characteristics and behavior, first described by Drs Meyer Friedman and Ray Rosenman in the 1950s. DUPAC's relaxation exercises are then presented, along with comments by Dr James A. Blumenthal of Duke University, who has conducted research in this area.

The DUPAC program is among the most respected of its kind, based on sound principles devoid of trendy components. It could receive no greater approbation than to be presented to the general public by a leading cardiologist and a respected medical writer. The authors have been scrupulously attentive in giving full credit to the medical researchers at Duke for the various topics discussed. In some instances they do so to the point of distracting the reader. But this is a small quibble. This book is a unique merger of an authoritative and highly readable discussion of heart disease and its causes as well as the DUPAC program for rehabilitating the victims of coronary artery disease. It is concise and well written and is highly recommended for both patients and physicians.

PASCAL JAMES IMPERATO, MD
Deputy Editor

In addition to these listings, the Journal *will publish obituaries written by physician readers. Inquiries should first be made to the Editor.*

Ernest V. Altman, MD, New York. Died May 4, 1984; age 81. Dr Altman was a 1928 graduate of Leopold Franzens-Universität Medizinische Fakultät, Innsbruck. He was a member of the American Psychiatric Association, the New York County Medical Society and the Medical Society of the State of New York.

Bernard Berglas, MD, New York. Died September 1, 1984; age 85. He was a 1925 graduate of Medizinische Fakultät der Universität, Wien. Dr Berglas was a Fellow of the American College of Surgeons and the American College of Obstetricians and Gynecologists, and a Diplomate of the American Board of Obstetrics and Gynecology. He was a member of the Academy of Medicine, the New York County Medical Society and the Medical Society of the State of New York.

John Brinkman, MD, Daytona Beach, Florida. Died January 1984; age 88. Dr Brinkman was a 1919 graduate of Jefferson Medical College of Philadelphia. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Ralph Edward Delbridge, MD, Rochester. Died August 17, 1984; age 80. Dr Delbridge was a 1930 graduate of the University of Buffalo Medical School. His memberships included the Academy of Medicine, the New York State Society of Internal Medicine, the American Geriatics Society, the Medical Society of the County of Monroe and the Medical Society of the State of New York.

Martin Delman, MD, Brooklyn. Died March 15, 1984; age 58. He was a 1958 graduate of the State University of New York Downstate Medical Center. Dr Delman was a Fellow of the American College of Surgeons and a Diplomate of the American Board of Ophthalmology. He was a member of the American Academy of Ophthalmology and Otolaryngology, the Medical Society of the County of Kings and the Medical Society of the State of New York.

Foster Taitt Drury, MD, Gouverneur. Died September 9, 1984; age 81. He was a 1936 alumnus of McGill University Faculty of Medicine, Montreal. Dr Drury was a member of the Medical Society of the County of St. Lawrence and the Medical Society of the State of New York.

Helen Elston, MD, Horseheads. Died July 16, 1984; age 89. Dr Elston was a 1927 alumna of Cornell University Medical College. She was a member of the Medical Society of the County of Tompkins and the Medical Society of the State of New York.

Terence Patrick Fogarty, MD, New York. Died September 19, 1984; age 55. He was a 1955 alumnus of Cornell University Medical College. Dr Fogarty was a Fellow of the American College of Surgeons and a Diplomate of the American Board of Ophthalmology. He was a member of the American Academy of Ophthalmology and Otolaryngology, the New York County Medical Society and the Medical Society of the State of New York.

Milton Howard Goolde, MD, Hastings-on-Hudson. Died September 13, 1984; age 80. He was a 1928 graduate of the State University of New York Downstate Medical Center. Dr Goolde was a member of the New York County Medical Society and the Medical Society of the State of New York.

Frederick G. W. Guggenbuhl, MD, Bronxville. Died September 13, 1984; age 84. He was a 1928 alumnus of New York Medical College, Flower and Fifth Avenue Hospitals. Dr Guggenbuhl was a member of the Bronx County Medical Society and the Medical Society of the State of New York.

Glenn Charles Hatch, MD, Clearwater, Florida. Died August 9, 1984; age 80. Dr Hatch was a 1928 alumnus of the University of Buffalo School of Medicine. He was a Fellow of the American Board of Surgeons and a member of the Medical Society of the County of Yates and the Medical Society of the State of New York.

Edward Jay Hornick, MD, New York. Died September 24, 1984; age 66. He was a 1943 alumnus of the University of Pennsylvania School of Medicine. Dr Hornick was a Diplomate of the American Board of Psychiatry and Neurology. His memberships included the American Psychoanalytic Association, the American Psychiatric Association, the New York County Medical Society and the Medical Society of the State of New York.

William M. Hummer, MD, Oneida. Died September 3, 1984; age 67. He was a 1943 graduate of the State University of New York Upstate Medical Center. Dr Hummer was a Fellow of the American College of Surgeons and a Diplomate of the American Board of Surgery. He was a member of the New York State Surgical Society, the Medical Society of the County of Madison and the Medical Society of the State of New York.

Michael P. Iancu, MD, New York. Died April 30, 1984; age 63. Dr Iancu was a 1948 alumnus of Universitatea din Bucureşti Facultatea di Medicină, Bucareşti. He was a member of the American Society of Nephrology, the Medical Society of the County of Kings and the Medical Society of the State of New York.

Max B. Kaplan, MD, Brooklyn. Died February 12, 1984; age 77. He was a 1937 graduate of Louisiana State University School of Medicine. Dr Kaplan was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

George Robert Kehoe, MD, Scotia. Died August 24, 1984; age 53. Dr Kehoe was a 1960 graduate of Creighton University School of Medicine. He was a member of the Medical Society of the County of Schenectady and the Medical Society of the State of New York.

Manes Kesten, MD, Flushing. Died August, 1983; age 86. Dr Kesten was a 1925 graduate of Medizinische Fakultät der Universität, Wien, and was a member of the Medical Society of the County of Tompkins and the Medical Society of the State of New York.

Benjamin Kogut, MD, West Islip. Died August 21, 1984; age 86. He was a 1920 graduate of the State University of New York Downstate Medical Center. Dr Kogut was a Fellow of the American College of Gastroenterology and the American College of Surgeons, and a Qualified Fellow of the International College of Surgeons. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Bernard Maurice Kroll, MD, Brooklyn. Died April 5, 1984; age 64. He was a 1944 alumnus of Wayne State University College of Medicine. Dr Kroll was a Diplomate of the American Board of Internal Medicine and a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Alexander Levine, MD, Brooklyn. Died September 15, 1984; age 74. He was a 1934 graduate of the State University of New York Downstate Medical Center. Dr Levine was a Fellow of the American Psychiatric Association and a Diplomate of the American Board of Psychiatry and Neurology. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

William Kenneth Major, MD, Waterloo. Died August 6, 1984; age 65. He was a 1944 alumnus of the University of Buffalo School of Medicine. Dr Major was a member of the Seneca County Medical Society and the Medical Society of the State of New York.

William A. Edwin Maloney, MD, Brooklyn. Died May 3, 1984; age 79. Dr Maloney was a 1930 alumnus of Georgetown University School of Medicine. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Arthur E. Mirkinson, MD, Roslyn. Died September 16, 1984; age 61. Dr Mirkinson was a 1947 graduate of Middlesex University School of Medicine. His memberships included the New York State Society of Internal Medicine, the Aerospace Medical Association, the American Society of Internal Medicine, the Nassau County Medical Society and the Medical Society of the State of New York.

Thomas Murphy, MD, Richmond Hill. Died February 21, 1984; age 71. Dr Murphy was a 1943 graduate of the State University of New York Downstate Medical Center. He was a Qualified Fellow of the International College of Surgeons. His memberships included the American Geriatrics Society, the American Society of Abdominal Surgeons, the Medical Society of the County of Queens and the Medical Society of the State of New York.

Alfred Irwin Myerson, MD, Cedarhurst. Died March 19, 1984; age 72. Dr Myerson was a 1938 alumnus of Baylor University College of Medicine. He was a member of the Medical Society of the County of Kings and the Medical Society of the State of New York.

Seymour Reissman, MD, Farmingdale. Died September 6, 1984; age 71. He was a 1934 alumnus of the State University of New York Downstate Medical Center. Dr Reissman was a Fellow of the American College of Surgeons and a Diplomate of the American Board of Orthopedic Surgery. His memberships included the Academy of Medicine, the American Academy of Orthopaedic Surgeons, the Nassau County Medical Society and the Medical Society of the State of New York.

Salvatore M. Romeo, MD, Rochester. Died August 22, 1984; age 57. Dr Romeo was a 1953 graduate of the University of Rochester School of Medicine and Dentistry. His memberships included the Academy of Medicine, the New York State Society of Internal Medicine, the American Geriatrics Society, the Medical Society of the County of Monroe and the Medical Society of the State of New York.

Richard W. Rommel, MD, Binghamton. Died August 29, 1984; age 72. He was a 1939 graduate of the University of Vermont College of Medicine. Dr Rommel was a Fellow of the American College of Surgeons and a Diplomate of the American Board of Surgery. He was a member of the Broome County Medical Society and the Medical Society of the State of New York.

Benjamin Charles Rosenthal, MD, New York. Died May 12, 1984; age 88. He was a 1920 graduate of the State University of New York Downstate Medical Center. Dr Rosenthal was a Fellow of the American College of Surgeons and a Diplomate of the American Board of Ophthalmology. His memberships included the New York Society for Clinical Ophthalmology, the American Academy of Ophthalmology and Otolaryngology, the Medical Society of the County of Kings and the Medical Society of the State of New York.

Lisbeth J. Sachs, MD, Riverdale. Died July 10, 1984; age 77. Dr Sachs was a 1934 alumna of Universität Bern Medizinische Fakultät. Her memberships included the New York Pathological Society, the American Psychiatric Association, the American Academy of Child Psychiatry, the American Society of Adolescent Psychiatry, the Medical Society of the County of Kings and the Medical Society of the State of New York.

Donald Johnson Simons, MD, New York. Died August 4, 1984; age 78. Dr Simons was a 1931 alumnus of Harvard Medical School. He was a member of the New York County Medical Society and the Medical Society of the State of New York.

Murray Spatz, MD, Flushing. Died September 19, 1984; age 57. Dr Spatz was a 1955 graduate of the State University of New York Downstate Medical Center. He was a member of the Medical Society of the County of Queens and the Medical Society of the State of New York.

George L. Tully, Jr, MD, Albany. Died August 31, 1984; age 65. He was a 1944 graduate of Tufts University School of Medicine. Dr Tully was a Diplomate of the American Board of Obstetrics and Gynecology, and a member of the Medical Society of the County of Albany and the Medical Society of the State of New York.

Guidelines for authors

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The *New York State Journal of Medicine* welcomes research papers and original essays on the practice of medicine, medical education, public health, the history of medicine, medicolegal matters, legislation, ethics, the mass media and socioeconomic issues in health care.

Manuscripts should be prepared according to the "Uniform requirements for manuscripts submitted to biomedical journals" (*NY State J Med* 1983; 83:1089–1094). The requirements were established by the International Committee of Medical Journal Editors, of which the *Journal* is a participating member. These Guidelines are intended to highlight aspects of the *Journal*'s particular style of publication.

A manuscript will be considered for publication if it is original, has not been published previously in whole or in part in either a medical journal or a lay publication, and is not simultaneously under consideration elsewhere. A copy of any possibly duplicative material, such as a reference "in press," should be submitted along with the manuscript.

PREPARATION

An original typewritten or "word-processed" manuscript and two photocopies (to facilitate outside review) are required. If the manuscript is not accepted for publication, the original and one copy will be returned. All figures must be submitted in triplicate. The manuscript should be double-spaced throughout, including references, tables, legends, quotations, and acknowledgments. A separate title page should include the full title of the paper in upper and lower case type, the names of the authors exactly as they should appear in print (including their highest academic degree), an abbreviated title of no greater than 40 spaces for use as a running foot, and the names of all providers of funding for research on which the paper is based. Information on the amount and allocation of funding is optional.

A corresponding author should be designated in the covering letter. Authors should list their title and affiliation at the time they did the work, and, if different, their present affiliation. The addresses and telephone numbers of all authors should be supplied for editorial purposes. All authors of a manuscript are responsible for having read and approved it for submission.

CATEGORIES

Research Papers should be limited to 2,500 words and should include the following sections: Introduction, Methods, Results, Discussion, and References. Multiple subheadings and numbered lists are discouraged. An abstract limited to 150 words should state the reasons for the study, the main findings, and their implications. Statistical evaluations should be described in the Methods section, and the name and affiliation of the statistician should be included in the acknowledgments if this individual is not listed as a coauthor. Reports of experiments involving human subjects must include a description in the Methods section of the informed consent obtained and a statement that the procedures followed were approved by an institutional research review committee. Anonymity of patients must be preserved. Reports of experiments on animals must note which guidelines were followed for the care and use of laboratory animals.

Case Reports should be limited to 1,250 words. Review Articles should not exceed 3,000 words. Commentaries should be between 750 and 1,000 words. Other kinds of original essays should not exceed 2,000 words. A letter of inquiry should be sent to the editor prior to submitting a Review Article or Commentary.

For Research Papers only, scientific measurements should be given in conventional units, with Système Internationale (SI) units in parentheses. Abbreviations and acronyms should be kept to a minimum, and jargon should be avoided. Generic names of drugs should be used instead of brand names.

FIGURES

The submission of color illustrations or slides is discouraged. Only black and white glossy photographic prints or "camera-ready" artwork will be accepted. The *Journal* is unable to provide art services such as the addition of arrows to photographs. A signed consent for publication must accompany photographs in which the patient is identifiable. Illustrations from other publications generally will not be considered. Legends for illustrations should be typed on a separate sheet, and for photomicrographs should include magnification and stain. Each illustration should be lightly marked on the back in pencil with the name of the first author, the number as cited in the text, and an arrow indicating the top. Each set of illustrations should be submitted unmounted in a separate envelope.

Tables should be simple, self-explanatory, and few in number. Each table should be typed double-spaced on a separate sheet.

REFERENCES

References should be limited to the most pertinent. The recommended maximum number of references is 25 for Research Papers and most other original contributions (except lengthier Review Articles), 12 for Commentaries and Case Reports, and six for letters to the editor.

Authors are responsible for the accurate citation of references. Citation of secondary sources is discouraged except where the original reference is unobtainable. Authors may not cite references they have not read, and the use of abstracts as references should be avoided.

References should be indicated in the text by superscript numbers following the name of the author (eg, Smith^2 reported two cases).

The list of references at the end of the article should be typed double-spaced and references should be numbered in the order in which they appear on the text. When there are six or fewer authors, all should be listed; where there are seven or more, the first three should be listed, followed by *et al.* Names of journals should be abbreviated according to *Index Medicus* and underlined.

Sample references:

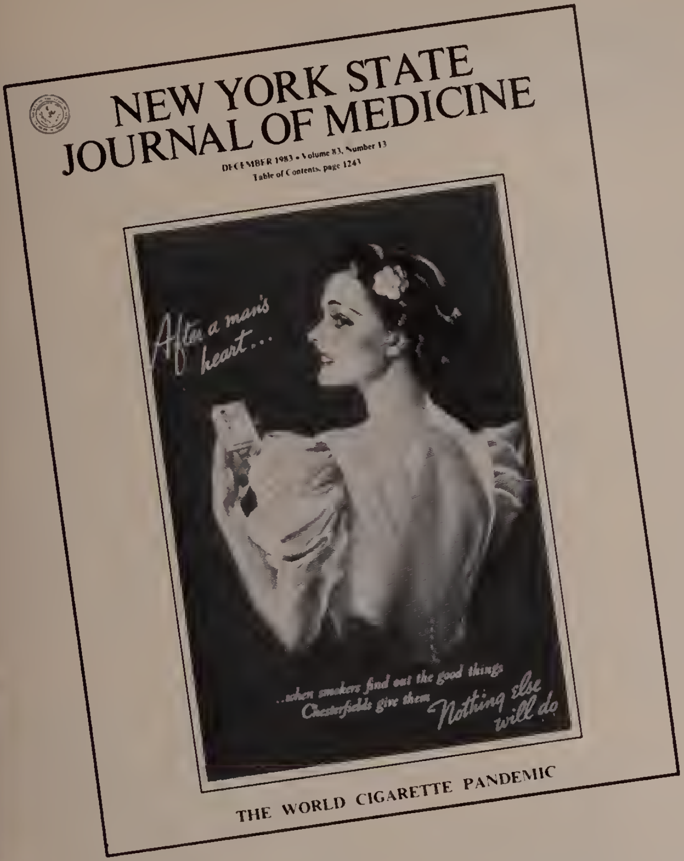
1. Kepes ER, Thomas P, Vemulapalli K: Methadone and intravenous morphine requirements. *NY State J Med* 1983; 83:925–927.
2. McGuigan JE. Peptic ulcer. In: Petersdorf RG, Adams RD, Braunwald E, Isselbacher KJ, Martin JB, Wilson JD, eds. *Harrison's Principles of Internal Medicine.* New York, McGraw-Hill, 1983, pp 1697–1712.

REVIEW

All manuscripts are reviewed by the editors, and most manuscripts are sent to outside referees. Decisions concerning acceptance, revision, or rejection of a manuscript are usually made within three to six weeks. Every effort will be made to assure prompt publication of an accepted manuscript. A galley proof will be sent to the author for approval prior to publication.

Address correspondence to Alan Blum, MD, Editor, *New York State Journal of Medicine*, P.O. Box 5404, 420 Lakeville Road, Lake Success, NY 11042.

The definitive analysis of the world cigarette pandemic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The New York State Journal of Medicine *cannot guarantee publication of meetings and lectures unless the information is submitted at least two months prior to the event.*

JANUARY 1985

AROUND THE STATE

MANHATTAN

Jan 9–June 26. **Internal Medicine Board Review.** 72 Cat 1 credits. Info: NYU Post-Graduate Medical School, 550 First Ave, New York, NY 10016. Tel: (718) 340-5295.

Jan 9–13. **Urological Pathology and Radiology.** Mount Sinai Medical Center. Info: Page & William Black Post-Graduate School of Medicine, One Gustave L. Levy Place, New York, NY 10029. Tel: (718) 650-6737.

Jan 17. **The Significance of Hemodynamic Measurement in Cardiological Practice.** Waldorf-Astoria Hotel. Info: New York Cardiological Society, 84 Grove St, Ste 2, New York, NY 10014. Tel: (718) 924-5346.

Jan 21. **A Symposium on the Health Care System into the 21st Century.** New York University. Info: Dr Ira Sohn, New York University Institute for Economic Analysis, 269 Mercer Street, New York, NY 10003. Tel: (212) 598-3413.

Jan 24–26. **Controversies in Obstetrics & Gynecology.** Grand Hyatt Hotel. Info: Patience A. Schenck, Postgraduate Course Administrator, The American College of Obstetricians & Gynecologists, 600 Maryland Ave, SW, Washington, DC 20024. Tel: (202) 638-5577.

BROOKLYN

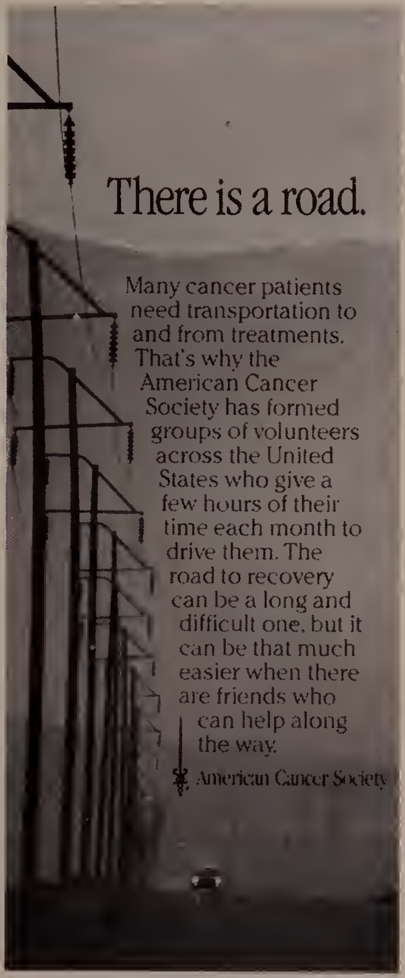
Jan 16. **Cutaneous T-Cell Lymphomas.** *Jan 23.* **Abnormalities of Platelet Function.** Info: Harvey Dosik, MS, Interfaith Medical Center, 555 Prospect Pl, Brooklyn, NY 11238. Tel: (718) 240-1000.

Jan 21. **The ABC's of ABG's.** 1 Cat 1 credit. *Jan 22.* **Hypoxia and its Consequences.** 1 Cat 1 credit. Info: Abraham I. Raskob, MD, CME, SUNY-Downstate Medical Center, Department of Anesthesiology, Box #6, 450 Clarkson Ave, Brooklyn, NY 11203. Tel: (718) 270-1934.

NASSAU

Jan 3. **Infections in Immunosuppressed Patients.** *Jan 10.* **Cutaneous Porphyrias.** *Jan 17.* **Prevention & Management of Influenza.** *Jan 24.* **Hemachromatosis.** *Jan 31.* **Current Concepts of Therapy in Rheumatoid Arthritis.** East Meadow. Info: Ethel A. Ford, CME Department of Medicine, Nassau County Medical Center, 2201 Hempstead Turnpike, East Meadow, NY 11554. Tel: (516) 542-4015.

Jan 23. **The Growing Concerns of the Growing Child: A Fresh Look.** 6 Cat 1 credits. Garden City Hotel. Info: Ann J. Boehme, Continuing Education Coordinator, LIJ-Hillside Medical Center, New Hyde Park, NY 11042. Tel: (718) 470-2114.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QUEENS

Jan 16–May 29. **Sixth Annual Internal Medicine Board Review Course.** 47½ Cat I credits. Jamaica. Info: Ann J. Boehme, Continuing Education Coordinator, LIJ-Hillside Medical Center/Queens Hospital Center Affiliation, New Hyde Park, NY 11042. Tel: (718) 470-2114.

SUFFOLK

Jan 8. **Classification & Treatment of Juvenile Rheumatoid Arthritis.** *Jan 15.* **Evaluation of the Child With Short Stature.** Huntington. Info: Arthur Schwager, MD, Pediatric CME, Huntington Hospital, 270 Park Ave, Huntington, NY 11743. Tel: (516) 427-0530.

Jan 16–June 12. **Advances and Update in Internal Medicine.** Stony Brook. Info: Tamarath K. Yolles, MD, CME, School of Medicine (HSC), 4L, Rm 177 SUNY at Stony Brook, NY 11794-8437, Tel: (516) 444-2094.

ROCKLAND

Jan 8. **Treatment of Mild to Moderate Hypertension.** *Jan 22.* **Hypercholesterolemia: Implications of the Coronary Primary Prevention Trial.** Nyack. Info: Myrna Hahn, Nyack Hospital, N. Midland Ave, Nyack, NY 10960. Tel: (914) 358-6200, ext 2509.

ST. LAWRENCE

Jan 10. **Cardiovascular Radiology.** Info: Sebastian A. Mazzotta, MD, Canton-Potsdam Hospital, 50 Leroy St, Potsdam, NY 13676. Tel: (315) 265-3300.

AROUND THE NATION

CALIFORNIA

Jan 7–11. **MRI, CT and Interventional Radiology.** 27 Cat I credits. San Francisco. Info: CME University of California School of Medicine, San Francisco, CA 94143. Tel: (415) 666-5731.

Jan 11–12. **Lasers for the Plastic Surgeon.** 7 Cat 1 credits. San Francisco. Info: Plastic Surgery Educational Foundation, 233 N. Michigan Ave, Ste 1900, Chicago, IL 60601. Tel: (312) 856-1818.

Jan 19–26. **Tutorial on Clinical Cytology.** Universal City. Info: 28th Tutorial on Clinical Cytology, University of Chicago, 5841 South Maryland Avenue, HM#449, Chicago, IL 60637. Tel: (312) 962-6569.

Jan 23–26. **Annual Review in Family Medicine: Controversies & Challenges in Primary Care.** San Francisco. Info: Extended Programs in Medical Education, University of California School of Medicine, Room 569-U, San Francisco, CA 94143. Tel: (415) 666-4251.

COLORADO

Jan 12–16. **Keystone Summit on Allergy, Immunology, Pulmonology, and ENT.** 19 Cat I credits. Keystone. Info: Helga Cole, National Jewish Hospital & Research Center, 3800 East Colfax Ave,

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Western New York State
Navy Medical Programs
Federal Building
111 West Huron Street
Buffalo, New York 14202
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Denver, CO 80206. Tel: (303) 398-1379.

Jan 17–19. **1985 Regional Scientific Meeting.** Colorado Springs. Info: American College of Physicians, 4200 Pine Street, Philadelphia, PA 19104. Tel: (215) 243-1200.

Jan 26–Feb 2. **Eleventh Annual Update in Hematology/Oncology.** Steamboat. Info: Office of CME, SUNY-Upstate Medical Center, 766 Irving Ave, Syracuse, NY 13210. Tel: (315) 473-4604.

Jan 28–Feb 1. **ENT Update for Primary Care Specialists.** Snowmass. Info: Cynthia Ashe, San Francisco Head and Neck Surgery Foundation, 350 Parnassus Ave, #502, San Francisco, CA 94117. Tel: (415) 221-8487.

MARYLAND

Jan 16–18. **Pericardiology 1985—The Pericardium: Its Diseases and Associations with Myocardial Diseases.** *Jan 23–25.* **Two-Dimensional and Doppler Echocardiographic Diagnosis of Congenital Heart Disease in Children.** Bethesda. Info: American College of Cardiology, 9111 Old Georgetown Road, Bethesda, MD 20814. Tel: (301) 897-5400, ext 241.

MASSACHUSETTS

Jan 13–25. **Program for Chiefs of Clinical Services.** Boston. Info: Harvard School of Public Health Office of Continuing Education. Dept. A 677 Huntington Ave, Boston, MA 02115. Tel: (617) 732-1171.

TEXAS

Jan 24–26. **Seventh Biennial Conference on Diseases of the Vulva and Vagina.** Houston. 20 Cat 1 credits. Info: Office of Continuing Education, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030. Tel: (713) 799-6020.

AROUND THE WORLD

BRAZIL

Jan 26–Feb 2. **First Annual Brazil/United States Anesthesiology Symposium.** Rio de Janeiro. Info: Medical Congress Coordinators, 1212 Avenue of the Americas, New York, NY 10036. Tel: (800) 223-5033.

MEXICO

Jan 14–18. **Diagnostic Radiology Seminars.** 32 Cat 1 credits. Ixtapa. Info: Radiology Postgraduate Education, University of California, Room C324, Third & Parnassus Ave, San Francisco, CA 94143. Tel: (415) 666-5731.

Jan 20–25. **Imaging of the Central Nervous System, Head and Neck, and Spine, Fourth Annual Comprehensive Update: CT, MR, Digital, Interventional.** 25 Cat 1 credits. Acapulco. Info: Betty Frost, CME, SUNY-Upstate Medical Center, 766 Irving Avenue, Syracuse, NY 13210. Tel: (315) 473-4606.

WEST INDIES

Jan 5–12. **Update in Cardiac Anesthesia and Surgery.** 14 Cat 1 credits. Antigua. Info: Page & William Black Post-Graduate School, One Gustave L. Levy Place, New York, NY 10029. Tel: (718) 650-6737.

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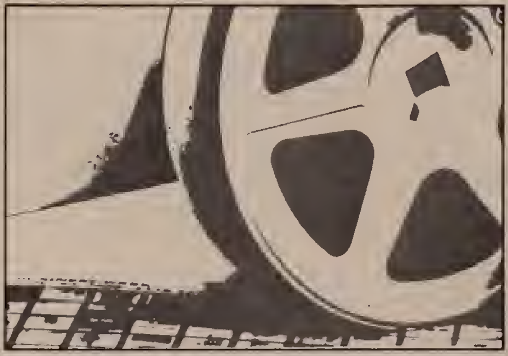

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INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential The significance of the membrane action in the treatment of arrhythmias is uncertain

The mechanism of the antimigraine effect of propranolol has not been established Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain.

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension, it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope INDERAL LA also improves exercise performance The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL

WARNINGS. CARDIAC FAILURE Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible)

> IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)— PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e g dobutamine or isoproterenol However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker In one case this resulted after an initial dose of 5 mg propranolol

PRECAUTIONS. *General:* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies

Beta adrenoreceptor blockade can cause reduction of intraocular pressure Patients should be told that INDERAL may interfere with the glaucoma screening test Withdrawal may lead to a return of increased intraocular pressure

Clinical Laboratory Tests Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DRUG INTERACTIONS Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity There were no drug-related tumorigenic effects at any of the dosage levels Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug

Pregnancy Pregnancy Category C INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose There are no adequate and well-controlled studies in pregnant women INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Nursing Mothers INDERAL is excreted in human milk Caution should be exercised when INDERAL is administered to a nursing woman

Pediatric Use Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy

Cardiovascular: bradycardia, congestive heart failure, intensification of AV block, hypotension; paresthesia of hands; thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia, visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics

Gastrointestinal. nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis

Allergic. pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress

Respiratory: bronchospasm.

Hematologic. agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported

Miscellaneous. alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained INDERAL LA should not be considered a simple mg for mg substitute for INDERAL INDERAL LA has different kinetics and produces lower blood levels Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval

HYPERTENSION—*Dosage must be individualized* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic The dosage may be increased to 120 mg once daily or higher until adequate blood-pressure control is achieved The usual maintenance dosage is 120 to 160 mg once daily In some instances a dosage of 640 mg may be required The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks

ANGINA PECTORIS—*Dosage must be individualized* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS)

MIGRAINE—*Dosage must be individualized* The initial oral dose is 80 mg INDERAL LA once daily The usual effective dose range is 160-240 mg once daily The dosage may be increased gradually to achieve optimum migraine prophylaxis If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued It may be advisable to withdraw the drug gradually over a period of several weeks

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use

*The appearance of INDERAL LA capsules is a registered trademark of Ayerst Laboratories

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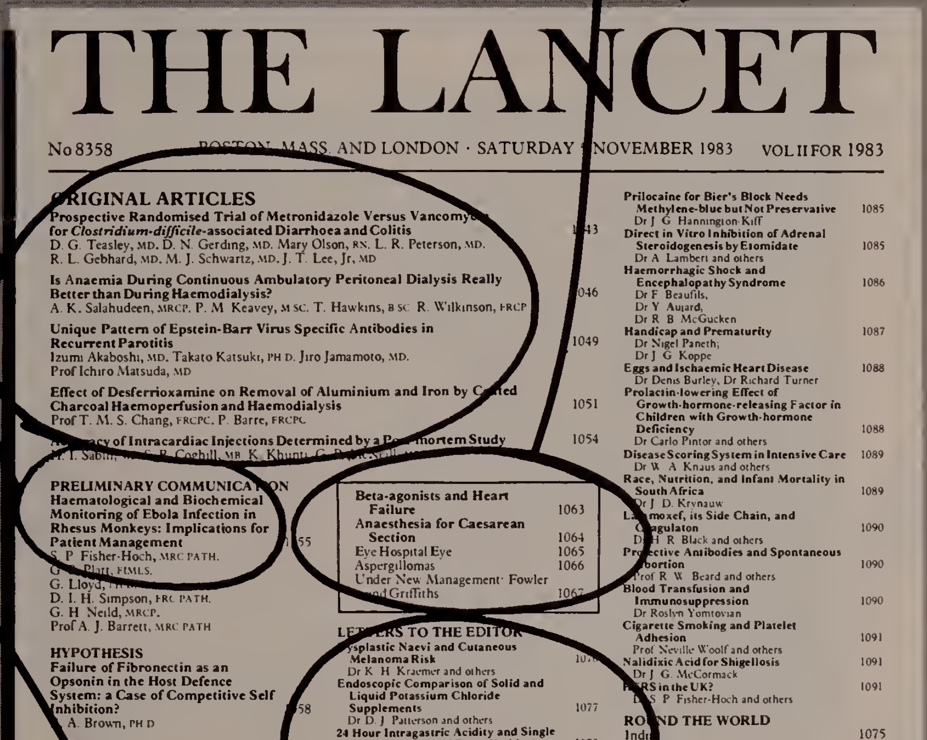

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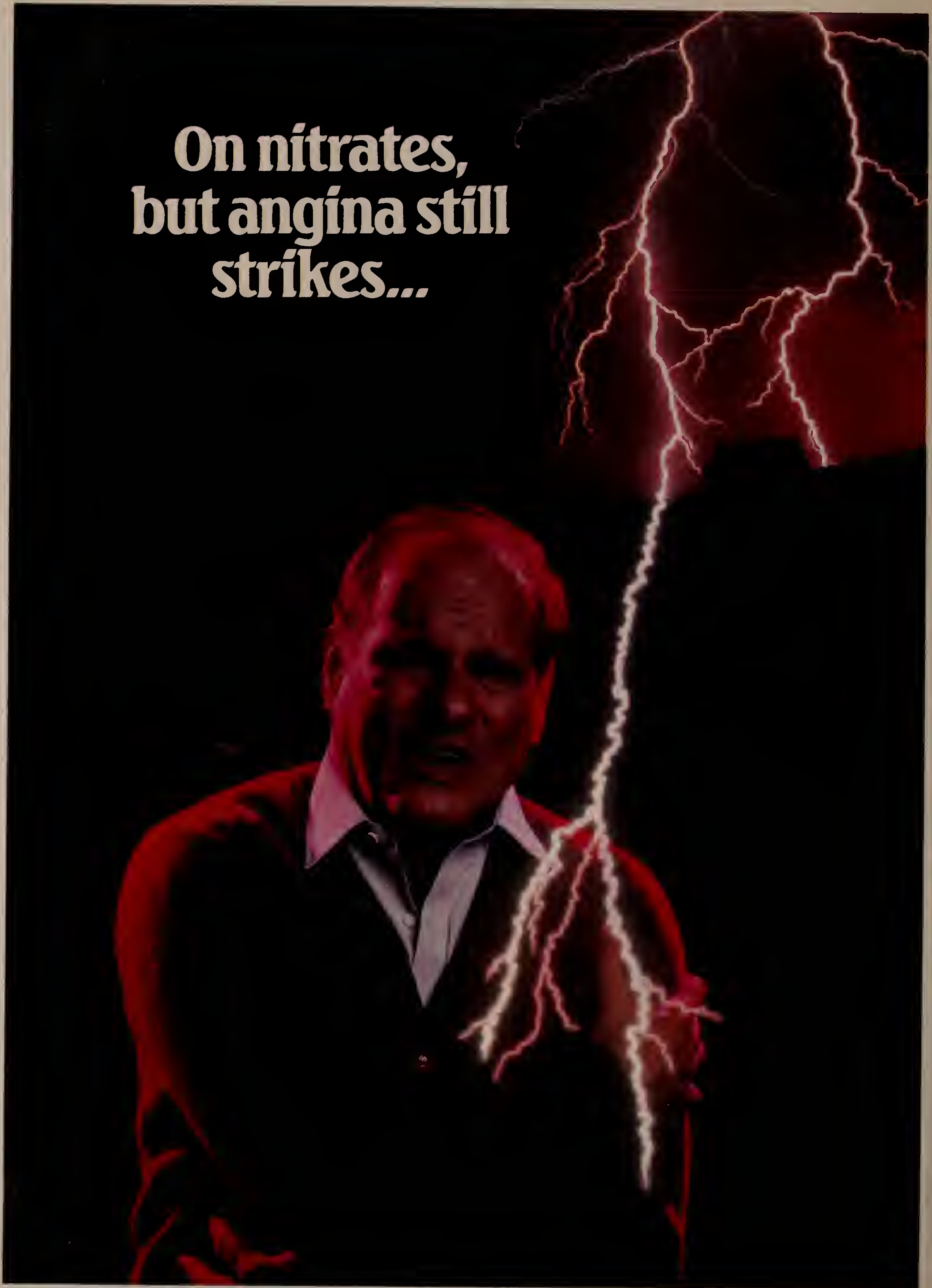
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Contraindications: Severe left ventricular dysfunction (see *Warnings*), hypotension (systolic pressure <90 mm Hg) or cardiogenic shock, sick sinus syndrome (if no pacemaker is present), 2nd- or 3rd-degree AV block. **Warnings:** ISOPTIN should be avoided in patients with severe left ventricular dysfunction (e.g., ejection fraction <30%) or moderate to severe symptoms of cardiac failure. Control milder heart failure with optimum digitalization and/or diuretics before ISOPTIN is used. ISOPTIN may occasionally produce hypotension (usually asymptomatic, orthostatic, mild, and controlled by decrease in ISOPTIN dose). Occasional elevations of liver enzymes have been reported; patients receiving ISOPTIN should have liver enzymes monitored periodically. Patients with atrial flutter/fibrillation and an accessory AV pathway (e.g., W-P-W or L-G-L syndromes) may develop a very rapid ventricular response after receiving ISOPTIN (or digitalis). Treatment is usually D.C.-cardioversion. AV block may occur (3rd degree, 0.8%). Development of marked 1st-degree block or progression to 2nd- or 3rd-degree block requires reduction in dosage or, rarely, discontinuation and institution of appropriate therapy. Sinus bradycardia, 2nd-degree AV block, sinus arrest, pulmonary edema, and/or severe hypotension were seen in some critically ill patients with hypertrophic cardiomyopathy who were treated with ISOPTIN. **Precautions:** ISOPTIN should be given cautiously to patients with impaired hepatic function (in severe dysfunction use about 30% of the normal dose) or impaired renal function, and patients should be monitored for abnormal prolongation of the PR interval or other signs of overdosage. Studies in a small number of patients suggest that concomitant use of ISOPTIN and beta blockers may be beneficial in patients with chronic stable angina. Combined therapy can also have adverse effects on cardiac function. Therefore, until further studies are completed, ISOPTIN should be used alone, if possible. If combined therapy is used, patients should be monitored closely. Combined therapy with ISOPTIN and propranolol should usually be avoided in patients with AV conduction abnormalities and/or depressed left ventricular function or in patients who have also recently received methyldopa. Chronic ISOPTIN treatment increases serum digoxin levels by 50% to 70% during the first week of therapy, which can result in digitalis toxicity. The digoxin dose should be reduced when ISOPTIN is given, and the patient carefully monitored. ISOPTIN may have an additive hypotensive effect in patients receiving blood-pressure-lowering agents. Disopyramide should not be given within 48 hours before or 24 hours after ISOPTIN administration. Until further data are obtained, combined ISOPTIN and quinidine therapy in patients with hypertrophic cardiomyopathy should probably be avoided, since significant hypotension may result. Adequate animal carcinogenicity studies have not been performed. One study in rats did not suggest a tumorigenic potential, and verapamil was not mutagenic in the Ames test. *Pregnancy Category C:* There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy, labor, and delivery only if clearly needed. It is not known whether verapamil is excreted in breast milk; therefore, nursing should be discontinued during ISOPTIN use. **Adverse Reactions:** Hypotension (2.9%), peripheral edema (1.7%), AV block: 3rd degree (0.8%), bradycardia: HR<50/min (1.1%), CHF or pulmonary edema (0.9%), dizziness (3.6%), headache (1.8%), fatigue (1.1%), constipation (6.3%), nausea (1.6%). The following reactions, reported in less than 0.5%, occurred under circumstances where a causal relationship is not certain: confusion, paresthesia, insomnia, somnolence, equilibrium disorders, blurred vision, syncope, muscle cramps, shakiness, claudication, hair loss, maculae, and spotty menstruation. Overall continuation rate of 94.5% in 1,166 patients. **How Supplied:** ISOPTIN (verapamil HCl) is supplied in 80 mg and 120 mg sugar-coated tablets. July 1982 2068

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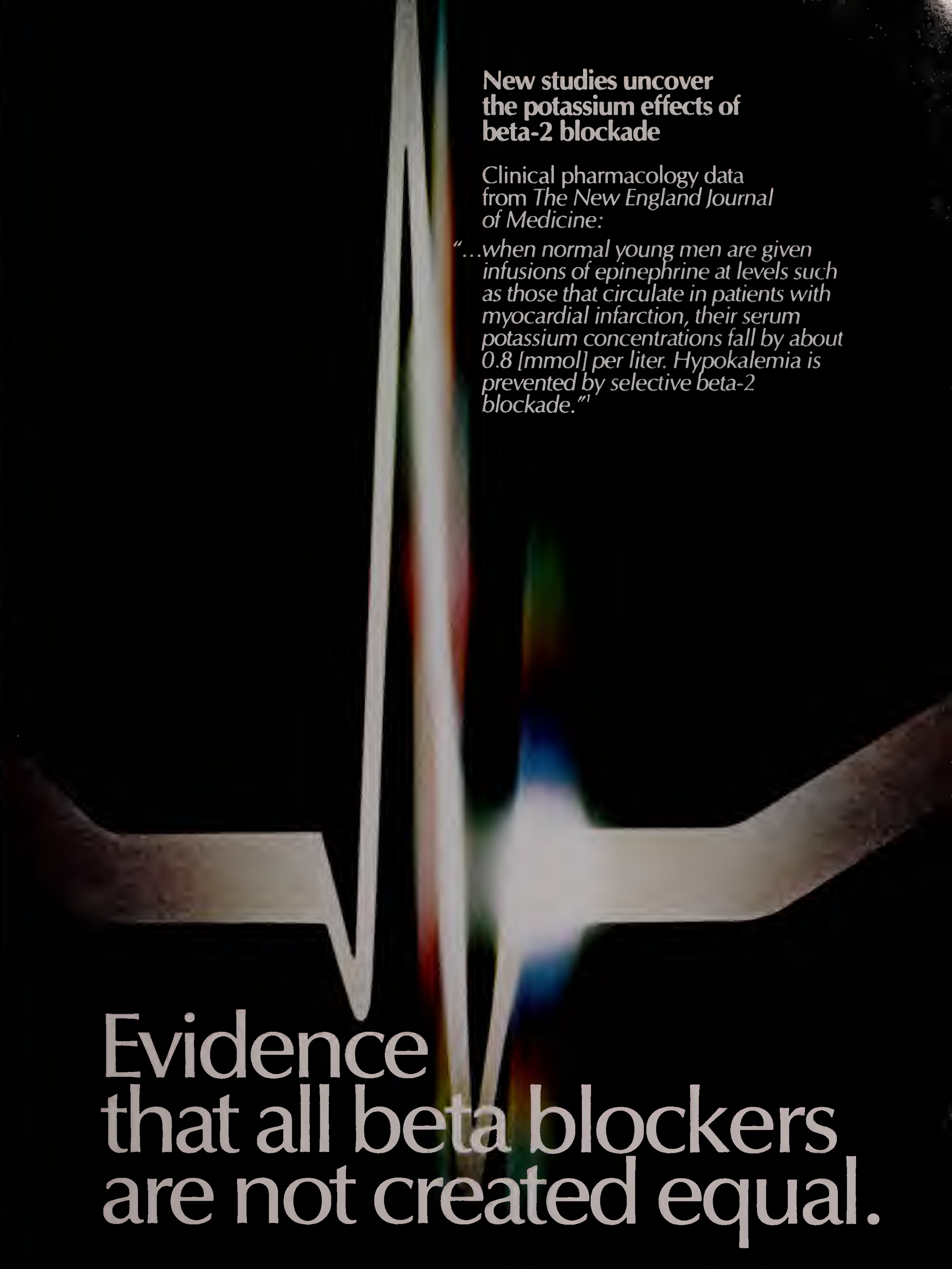

New studies uncover the potassium effects of beta-2 blockade

Clinical pharmacology data from *The New England Journal of Medicine:*

"...when normal young men are given infusions of epinephrine at levels such as those that circulate in patients with myocardial infarction, their serum potassium concentrations fall by about 0.8 [mmol] per liter. Hypokalemia is prevented by selective beta-2 blockade."[1]

Evidence that all beta blockers are not created equal.

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in hypertension…

Once-daily INDERAL LA (propranolol HCl) for smooth blood pressure control without the potassium problems of diuretics

Once-daily INDERAL LA (propranolol HCl) avoids the risk of diuretic-induced ECG abnormalities due to hypokalemia.[2,3] In addition, INDERAL LA preserves potassium balance without additive agents or supplements while providing simple, well-tolerated therapy with broad cardiovascular benefits.

Once-daily INDERAL LA for the cardiovascular benefits of the world's leading beta blocker

Simply start with 80 mg once daily. Dosage may be increased to 120 mg to 160 mg once daily as needed to achieve additional control.

Like conventional INDERAL tablets, INDERAL LA should not be used in the presence of congestive heart failure, sinus bradycardia, heart block greater than first degree, and bronchial asthma.

For beta-1/beta-2 blockade

Once-daily

INDERAL LA

(PROPRANOLOL HCl) *LONG ACTING CAPSULES*

The appearance of these capsules is a registered trademark of Ayerst Laboratories

80 mg 120 mg 160 mg

Please see brief summary of prescribing information on the next page for further details.

Once-daily
For beta-1/beta-2 blockade INDERAL® LA
(PROPRANOLOL HCl) LONG ACTING CAPSULES

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is a registered trademark
of Ayerst Laboratories

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR)*

INDERAL® LA brand of propranolol hydrochloride **(Long Acting Capsules)**

DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules

CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product INDERAL LA can provide effective beta blockade for a 24-hour period

The mechanism of the antihypertensive effect of INDERAL has not been established Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use Effects on plasma volume appear to be minor and somewhat variable INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential The significance of the membrane action in the treatment of arrhythmias is uncertain

The mechanism of the antimigraine effect of propranolol has not been established Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient But there are also situations in which sympathetic stimulation is vital For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm

Propranolol is not significantly dialyzable

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension, it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic INDERAL LA is not indicated in the management of hypertensive emergencies

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope INDERAL LA also improves exercise performance The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation Clinical improvement may be temporary

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL

WARNINGS. CARDIAC FAILURE Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure and its inhibition by beta blockade may precipitate more severe failure Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure Therefore, at the first sign or symptom of heart failure the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible)

> IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)— PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors

MAJOR SURGERY The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta receptor agonists and its effects can be reversed by administration of such agents, e g dobutamine or isoproterenol However such patients may be subject to protracted severe hypotension Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers

DIABETES AND HYPOGLYCEMIA Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes In these patients, it may be more difficult to adjust the dosage of insulin

THYROTOXICOSIS Beta blockade may mask certain clinical signs of hyperthyroidism Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm Propranolol does not distort thyroid function tests

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker In one case this resulted after an initial dose of 5 mg propranolol

PRECAUTIONS. *General* Propranolol should be used with caution in patients with impaired hepatic or renal function INDERAL (propranolol HCl) is not indicated for the treatment of hypertensive emergencies

Beta adrenoreceptor blockade can cause reduction of intraocular pressure Patients should be told that INDERAL may interfere with the glaucoma screening test Withdrawal may lead to a return of increased intraocular pressure

Clinical Laboratory Tests. Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase

DRUG INTERACTIONS Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity There were no drug-related tumorigenic effects at any of the dosage levels Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug

Pregnancy Pregnancy Category C INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose

There are no adequate and well-controlled studies in pregnant women INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Nursing Mothers INDERAL is excreted in human milk Caution should be exercised when INDERAL is administered to a nursing woman

Pediatric Use Safety and effectiveness in children have not been established

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy

Cardiovascular bradycardia congestive heart failure, intensification of AV block, hypotension, paresthesia of hands thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type

Central Nervous System lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics

Gastrointestinal nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis

Allergic pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress

Respiratory bronchospasm

Hematologic agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura

Auto-Immune In extremely rare instances, systemic lupus erythematosus has been reported

Miscellaneous alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained INDERAL LA should not be considered a simple mg for mg substitute for INDERAL INDERAL LA has different kinetics and produces lower blood levels Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic The dosage may be increased to 120 mg once daily or higher until adequate blood pressure control is achieved The usual maintenance dosage is 120 to 160 mg once daily In some instances a dosage of 640 mg may be required The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks

ANGINA PECTORIS—*Dosage must be individualized* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily In angina pectoris the value and safety of dosage exceeding 320 mg per day have not been established

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS)

MIGRAINE—*Dosage must be individualized* The initial oral dose is 80 mg INDERAL LA once daily The usual effective dose range is 160-240 mg once daily The dosage may be increased gradually to achieve optimum migraine prophylaxis If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued It may be advisable to withdraw the drug gradually over a period of several weeks

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use

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9411/1184

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NEW YORK STATE JOURNAL OF MEDICINE

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Volume 84
January–December
1984

Editor:
Alan Blum, MD

Deputy Editor:
Pascal James Imperato, MD

Published by the
MEDICAL SOCIETY OF THE STATE OF NEW YORK
PO Box 5404
420 Lakeville Road
Lake Success, NY 11042

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CLASSIFICATION CODES

CPC = Clinicopathologic Conference
CR = Case Report
ED = Editorial Commentary
HIST = History of Medicine
LE = Letter to the Editor
NF = News Feature
RPC = Correlation Conference in Radiology and Pathology

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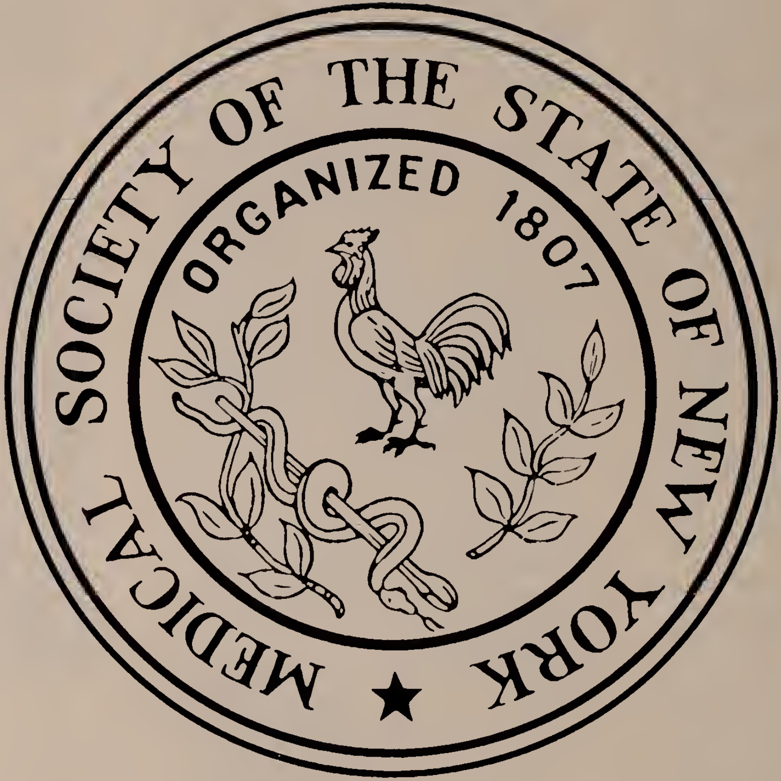
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